

The Role of Branding and Pricing on Health Outcomes via the Placebo Response

by

Rebecca L. Waber

B.S. Biopsychology
Tufts University, 2006

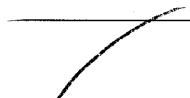
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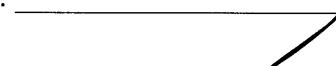
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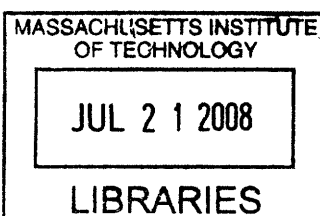

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ABSTRACT

Marketing factors such as pricing and branding are known to affect people's judgments and expectations regarding a product. When the product in question is a medical treatment, this effect may modify the placebo response. As the placebo response modifies the overall effect of the treatment in an additive manner, this implies that marketing factors may have a direct effect on medical outcomes, particularly in disorders that have large placebo effects. This thesis explores this idea. First a laboratory study is presented that used electric shocks and a placebo pill to demonstrate that a price discount may reduce the efficacy of a placebo analgesic. A second laboratory study, using the cold pressor test and a medication with low non-placebo efficacy, failed to demonstrate superiority of a brand-name over generic medication in terms of cold tolerance or pain ratings, but the brand-name did lead to quicker habituation to the cold pain. In addition, quantitative and qualitative research exploring attitudes held towards generic medications shows conflicted beliefs and a lack of complete trust in generic medications in both general and geriatric populations. "Non-commercial" forms of marketing, including the labeling of, and description of, a disorder, are also touched upon. The implications of this research for marketing are discussed, as well as necessary steps for the research development of this field.

Thesis Supervisor: Dan Ariely

Title: Professor of Media Arts and Sciences, Professor of Marketing

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Rebecca L. Waber

The Following Served As Readers

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Background

Introduction

When ‘marketing’ and ‘healthcare’ are spoken of together, the two fields are typically thought of as, if not directly at odds with each other, then at least partners in an uneasy relationship. The discussion is typically concerned with the effect of direct-to-consumer advertising on prescribing habits or the biasing effect of pharmaceutical company gifts. These are, of course, very important research topics.

However, there exists another potential link between marketing and healthcare which has not been well examined. Marketing factors, such as pricing and branding, are well known to influence perception and expectation. Since expectation and beliefs are the main drivers of the placebo response, it is possible that marketing factors may modify the placebo response. Because the placebo response is an important component of many medical outcomes, it is logical to postulate that a manipulation of price or brand could have a direct effect on medical outcomes by modifying the placebo response. This issue has not before been raised by medical or psychological research, but the potential public health effect could potentially be quite significant and therefore demands research attention.

The goal of this thesis is to initiate research on this topic. Two laboratory experiments and several questionnaire and interview based studies are presented in order to take the first steps in considering the direct role of commercial information on health outcomes.

Expectation and narrative

The ‘gold standard’ blind clinical trial is designed to create an impartial testing system which allows only specifically efficacious treatments to make it into the medical marketplace, and this system has been effective in creating many vital medical advances. Another implication of our reliance of this system, however, is the denial of the role of myth, ritual, and non-specific healing in modern medicine. Accordingly, the role of the placebo effect in medical treatments has often been looked upon unfavorably (de Craen, Kaptchuk, Tijssen, & Kleijnen, 1999).

The placebo effect can have negative connotations, conjuring up images of 19th-century snake oil sellers or primitive religious healing rituals. However, a great number of products thrive today which are not FDA tested or approved (herbal supplements, diet pills, and so on), and the concept of ‘evidence-based’ medicine remains a hot topic of discussion rather than being naturally embedded in the consciousness of practitioners. In fact, the question of to what extent healing can relate to myth and ritual in modern medicine is a fascinating one (Kaptchuk, 2002). A 1944 article by Cannon was perhaps the first well-known paper to suggest such a link, discussing the anthropological concept of ‘voodoo death’ (or the ability of a ‘curse’ to cause death). He posited that the phenomenon might be authentic, having a corollary with instances in modern medicine such as when someone dies, for instance from shock, without any visible cause for death (Cannon, 1957). He speculated that acute fear might cause such a result (Sternberg, 2002).

Another fascinating article on the potential relationship between ritual and modern medicine is a case report by Dr. Clifton Meador. The first case involved voodoo death. A patient seemed to be dying, barely conscious, apparently following a curse by a voodoo priest. The physician performed a ritual within the context of the curse, which was followed by the recovery of the patient. Instead of confining such a situation to a certain foreign culture, Dr. Meador went on to describe what he considered a possible comparable situation, the case of a patient in a mainstream medical setting who was diagnosed with esophageal cancer. The patient and all the doctors firmly believed he would die soon, but autopsy was unable to find a cause of death, the cancer diagnosis apparently being a false positive (Meador, 1992).

Finally, Dr. Herbert Spiegel reported an anecdote in a modern Catholic hospital, in which a priest mistakenly gave last rites to the wrong patient, who died quickly thereafter (Spiegel, 1997). Other such anecdotes exist (Weisman & Hackett, 1961), but articles on this topic appeared for the most part in the 1950s and 60s, under the influence of psychoanalysis, and have not been much seriously considered since. Naturally, as anecdotes these stories must be approached with caution, and yet they are thought-provoking. The assumption that our medical system has cut its ties to the human imagination is appealing but perhaps overzealous.

It is interesting to consider what form modern superstitions might take. Arguably, some of these superstitions could be cognitive heuristics relating to issues like price-quality assumptions, belief in brand names, or the effect of disease labels.

On the issue of price-quality assumptions, there are corollaries from other traditions. Traditional healing substances are often those that are difficult to obtain and expensive, such as rhino horn or tiger bone (Bensky, 1986). And in Reiki, a spiritual healing practice involving the transfer of energy through the hands, a traditional caveat is that money must be charged in order for clients to value the treatment enough for it to work. One Reiki practitioner asked about this idea agreed that in everyday practice this condition seemed to be accurate, and that that charging more implied that the healer's services were worth more, which led to obtaining the same healing result in less time (Director, Reiki Center of Greater Washington, personal communication, April 16 2008).

To date however, there has not been much research on the role of prices or marketing on the placebo effect and medical treatments specifically, although the idea that direct-to-consumer advertising might produce a useful placebo effect was actually posited in one 2006 paper (Almasi, Stafford, Kravitz, & Mansfield, 2006). In addition, one recent anthropology thesis analyzed in depth the relationship that patients can have with their medications, particularly as a result of direct-to-consumer advertising and branding (Greenslit, 2005). There is also some evidence that the enhanced effectiveness of antidepressant drugs over the past few decades could be a response to increased marketing and societal faith in the drugs (Walsh, 1983).

In essence, the role of marketing, myth, and ritual is one of epistemology. Is the value of a medical product established solely through clinical trial results, or do people in the real world assign additional value to it as a function of heuristics of prices, brands, and other informational signals?

The Placebo Effect

Introduction to the Placebo Effect

The placebo effect may be one of the most powerful underappreciated forces in medicine. To begin with, when discussing these effects, it's important to keep terminology clear. A placebo itself, such as the classic 'sugar pill,' may help engender placebo effects. However, it is not the pill itself causing the reaction, but rather the significance and meaning involved in taking the pill. This is why Dr. Daniel Moerman, a well-known researcher on the placebo effect, argues that a better term for the phenomenon would be "meaning effects (D. E. Moerman & Jonas, 2002)." Studying the placebo effect essentially means studying the psychosocial context surrounding a medical treatment (Colloca & Benedetti, 2005).

Placebo effects have long played a key role in medicine. For thousands of years many medical treatments were without specific objective effect and thus relied exclusively on placebo responses. While the mechanism underlying placebo responses differs with the ailment, placebos still play an important role in medicine. Strong placebo effects have been demonstrated in many conditions, including coronary artery disease (Granger et al., 2005), depression (Leuchter et al., 2004), pain (Price et al., 1999), Parkinson's disease (Pollo et al., 2002), irritable bowel syndrome (Patel et al., 2005), and many others (Koshi & Short, 2007). Imaging technologies, behavioral studies, and clinical data have shown that responsiveness to placebo reflects physiologic changes in the body, such as endorphin activation in the case of analgesia (Zubieta et al., 2005), and can thus be thought of as the body recruiting its healing abilities in response to beliefs and expectations (Brody, 2000).

The implications of the placebo effect are not limited to treatments with placebos. (In fact, knowing that one is taking a placebo would naturally decrease the placebo response produced by it), and strong effects can also be found with medications, medical devices (Long, Uematsu, & Kouba, 1989), and physical manipulations (Kaptchuk, Goldman, Stone, & Stason, 2000). Although the archetypical placebo is the sugar pill, there are many other types of placebos. Irrespective of the type of treatment, the placebo effect occurs when the patient believes that an experience will help their condition. Back in the 1950s, a treatment for angina called mammary artery ligation was popular; doctors and patients reported considerable success with the procedure. However, after a double-blind clinical trial utilizing sham surgery for one group of patients showed no greater efficacy for the procedure over the placebo surgery, the procedure was abandoned. To most people, this experiment simply demonstrated that the well-liked ligation procedure was a failure, but it is also a striking example of the power of placebo. All the patients believed they would be helped by the procedure, and they were, in terms of needing less

nitroglycerin and increasing their exercise tolerance (Cobb, 1959 as cited in (D. Moerman, 2002). In addition to demonstrating the ineffectiveness of mammary artery ligation, this story showcases the usefulness of placebo.

Context Effects

The placebo effect is not constant. Actually, there can be remarkable variability in a placebo response even when considering the same treatment for the same disease (D. E. Moerman, 2000). Placebo responses can be quite strong, but they are also extremely sensitive to contextual factors in the environment, and can thus vary considerably across situations. Factors that have been shown to modulate the placebo response physician attitude, confidence, belief in the drug (Thomas, 1987) (Gracely, Dubner, Deeter, & Wolskee, 1985), and even the color of the pill (such as red pills being better as stimulants than depressants, to go along with usual meanings of those colors) (Blackwell, Bloomfield, & Buncher, 1972) (Lucchelli, Cattaneo, & Zattoni, 1978).

Expectations and the meaning of contextual effects drive the placebo response (Koyama, McHaffie, Laurienti, & Coghill, 2005) (Colloca & Benedetti, 2005). For instance, a person might have stronger expectations for a medication that is administered via an injection rather than a pill, given in a hospital rather than at the local doctor's office, or when the physician's attitude toward the medicine is enthusiastic rather than ambivalent (Benedetti, 2002). These and others factors influence what the patient anticipates and accordingly influence the overall efficacy of the treatment.

Additional evidence that placebo effects are a result of expectation are that Alzheimers' patients, as well as people who do not know that they are being given a medication, do not experience these effects (Benedetti et al., 2006), (Kirsch, 2003), and that surreptitiously reducing the pain of the treatment while giving a placebo will consequently imbue that placebo with pain-reducing abilities (Price et al., 1999).

Placebo effects have been viewed and used in very different ways across history and cultures, from acceptance to skepticism and from viewing it as a positive phenomenon to a negative one (de Craen et al., 1999). The negative reputation is often related to the idea that placebo effects interfere with finding real drug effects, since clinical trials are based upon comparing placebo and active groups. The negative view of the placebo effect had been the dominant view of the placebo effect for the past several decades. However, recently, some researchers and clinicians have become interested in harnessing the placebo effect for patient well-being.

Nocebo

Placebo effects are most commonly thought of in connection to healing, but placebo effects are not necessarily in a positive direction. Belief and expectation can just as readily be harmful to health. This negative action is sometimes called the nocebo effect, but it is simply another incarnation of the placebo effect. The same treatment, with a different expectation, can produce wildly different effects. In one classic experiment, a physician gave subjects either ipecac (which causes vomiting) or atropine (which soothes

the stomach). He used a tool inserted into the stomach so that he could actually visualize the effects of the medicines. Then he gave his subjects an inactive substance and told them either that it was ipecac or that it was atropine, and actually watched the stomach wave patterns behave in accordance with their expectations. In one patient, he even gave ipecac saying it was atropine, and vice versa, and observed the stomach wave patterns match expectation instead of chemistry (Brody, 2000).

Adverse drug effects are an extremely important issue, as they can spell the end to otherwise successful pharmaceuticals. However, it is difficult to disentangle placebo from specific side effects, particularly because even no-treatment (people given no treatment of any kind, including placebo treatment) control subjects will often report having symptoms when asked about them. Therefore, no-treatment control conditions are not often performed, making it difficult to know how far above baseline reported negative side effects really are (Khosla, Bajaj, Sharma, & Mishra, 1992).

Placebo treatments can lead to unwanted side effects or adverse drug effects. Just as with positive placebo effects, nocebo effects rely on suggestion and expectation of adverse or weak results. For example, in one study that investigated the way that information is presented to patients in the context of influenza vaccination, framing the risk of side effects negatively (as the percentage of people who experience a side effect resulting from the vaccination) versus positively (as the percentage of people who don't experience a side effect), increased the presence of both side effects and work absenteeism after the immunization (O'Connor, Pennie, & Dales, 1996). Also, side effects reported from a placebo increase with increasing dosage of the placebo (Pogge & Coats, 1962).

One tricky issue arising from this problem is how physicians and pharmaceuticals should present risks to patients. Naturally, people must be informed about risks in order to make decisions, but knowing too many details about risks, or learning about them about them in emotional ways, may increase the likelihood that the medication will not be tolerated by the patient. This question is related to philosophical issues in bioethics and informed consent.

In the bioethics literature and the Declaration of Helsinki, the three central concepts are respect for persons, beneficence, and justice ("Declaration of Helsinki (1964)," 1996). The American bioethics community has put a particular focus on respect for persons, which has been taken to mean informed consent. However, less effort is put into understanding the optimal way to present informed consent information to patients to ensure A) appropriate understanding and B) avoid undue anxiety, possibly leading to increased nocebo effects.

One study showed that patients who were given an informed consent document that detailed the possible risks, versus one that didn't go through the specific risks, increased patient anxiety as reported on the Spielberger State-Trait Anxiety Inventory. Perhaps even more worrisome, more people needed anxiolytic as administered by a nurse blinded to the subject's condition in the study (Goldberger, Kruse, Parker, & Kadish, 1997). This is worrisome because of the possibility of increasing side effects by highlighting possible

negative consequences. Also problematic is that, given the option, people will generally opt to receive more information even when it is not in their best interest because of people's inability to forget or discount information they have previously learned (Camerer, 1989). In the same study, subjects were asked afterwards how satisfied they were with the informed consent document they had received. The people who were given the detailed risks were happy having received those details, but the people who didn't get those details were also satisfied. They did not say they wished they had more details.

The philosophical issue of respect for persons is an important one, but it is also something that should be debated with a full understanding of where a narrow focus on informed consent as a panacea can go wrong. Without resorting to the severe paternalism that casts such a shadow over medicine of the 1950s and 60s (Vinar, 1969), it should still be possible to empower people by crafting consent forms in such a way as to provide them with risk and benefit information in the way most beneficial for their own cognitive processing and use, and not merely using informed consent forms as an afterthought, or worse, as merely legal protection.

Physiology

A misconception about the placebo response is that only 'imagined' symptoms can be alleviated by a placebo. In fact, placebos work by engaging the body's own biochemical healing systems. In placebo analgesia, incoming sensory information combines with expectation in the brain to shape the experience of pain (Koyama et al., 2005). fMRI studies show that placebo analgesia is related to decreased brain activity in pain-reporting regions of the brain, including the thalamus, insula, and anterior cingulate, as well as increased activity in the prefrontal cortex, implying that the experience of pain is being altered (Wager et al., 2004). Many of the body's hormones and neurotransmitters affect healing and may be implicated in placebo responses. It is known that placebo analgesia is mediated at least in part by endorphins effect on the μ -opioid system, a pain and stress inhibitory neurotransmitter system. As another example, a recent paper by Benedetti and Colloca reviews how anxiety may increase pain-related nocebo effects by the activation of the cholecystokinergic (CCK) system, which facilitates pain transmission (Colloca & Benedetti, 2007). In this manner, placebo effects reflect a fascinating interplay between the psychological and the neurological. Other placebo effects (non-analgesia related) work through different neural mechanisms (Fricchione & Stefano, 2005) (Pacheco-Lopez, Engler, Niemi, & Schedlowski, 2006) (de la Fuente-Fernandez et al., 2001) but the current discussion will focus only on pain.

The question of why some individuals demonstrate stronger placebo effects than others has long been a research topic, and in fact for several decades clinical trial researchers attempted to use personality factors to exclude 'placebo responders' from trials, to seemingly increase the drug effect. However, personality factors were never found to be reliable for this purpose, and it is now believed genetically determined variation in opioid response may be a large player in interpersonal variation (Ikeda et al., 2005).

Additivity

It should be clear by now that ‘the placebo effect’ is not restricted to inactive placebos. Many medical treatments act in two ways concurrently. The first is the way described in the relevant pharmacology or surgery textbook for that condition, and the second is the placebo effect. Both of these effects are mediated biochemically, and both of these responses in conjunction with each other are responsible for the improvement seen after a medical treatment. Many researchers believe that a significant portion of the effects of medicines, from anti-histamines to blood pressure drugs, are due to this second effect (placebo). For some types of treatment, expectation may even make up the majority of the effect; researchers have determined that of the six leading anti-depressants, approximately 80% of their effect was duplicated in placebo control groups (Kirsch et al., 2008), (Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008).

The placebo effect is generally considered to be additive with non-placebo drug effects. This is in fact the underlying assumption of all clinical trials, since the drug effect is taken to be the difference between the placebo and active groups. Therefore the total effect of a medical treatment can be thought of schematically as the sum of the non-placebo specific effect and any positive placebo effects, minus any nocebo effects (Kaptchuk et al., 2008).

This is not necessarily an endorsement of using pure-placebo treatments, especially because many such treatments’ placebo benefits may be overshadowed by risk. Blood-letting or mercury-based medications may have had important placebo effects, but their danger outweighed it. Similarly some placebo treatments could contain other risks, and even when they don’t, there are ethical questions involved in prescribing placebos. In addition, if prescribing placebos becomes a known practice, this could introduce doubt in treatments and reduce placebo effects. Therefore, the relevant question is to understand how to enhance the placebo *component* of a treatment for overall improved medical outcomes.

The placebo effect in clinical trials

As mentioned earlier, the ‘gold standard’ of modern medical research is taken to be the two-armed blinded trial consisting of a placebo and active condition. The role of placebo effects in clinical trials is not as simple as is sometimes assumed because of the fact that placebo effects are not constant background noise. One major issue is that clinical trials inform patients that they may not be receiving the real treatment, and that 50% of them will receive the placebo. This information is believed to alter subject response to the treatment by reducing placebo effects through encouraging doubt. One study by Kirsch and Weixel gave participants decaffeinated coffee, telling them either that there was a 50% chance of them receiving placebo or active caffeine (mimicking double-blind conditions), or telling them that they would receive caffeine (deceptive condition). The two conditions led to significantly different results, with only the deceptive condition leading to an increase in pulse rate (Kirsch & Weixel, 1988). In double-blind clinical trials, the placebo effect may be so significant that the most relevant discriminating factor between subjects is not what group they were assigned to, but rather what group they have guessed they are in, making perceived group assignment a very relevant factor to attend to (McRae et al., 2004) (Bausell, Lao, Bergman, Lee, & Berman, 2005).

In contrast to clinical trials, many experimental trials use deception and do not tell subjects that they may receive a placebo. The American Psychological Association has specific guidelines for when research may use deception, mandating that the study must have value that cannot be learned without deception, and that the subject must be 'debriefed' with the truth at the end of the research ("The Ethical Principles of Psychologists and Code of Conduct," 2003). However, deception is typically not appropriate in a clinical setting. Another option that avoids deception is to use the hidden administration of a drug. The patient consents to getting the drug, but is not aware of when. By administering the drug through an already-existing intravenous catheter, it is possible to examine the effects of the drug independent of placebo effects (Kirsch, 2003).

Pain

Strong and clinically relevant placebo effects have been studied in many conditions, as discussed earlier. The best-studied of these, however, is pain. Placebo analgesia is probably the most well-known and understood placebo pathway, and as early as the 1970s researchers were coming to understand the importance of endogenous opioids in creating placebo analgesia by observing that the opioid antagonist naloxone could partially prevent the placebo response (Grevert, Albert, & Goldstein, 1983), (Levine, Gordon, & Fields, 1978).

The laboratory experiments discussed here focus on placebo analgesia for several reasons. First, it is the best studied placebo effect, and the one for which the neural mechanisms are best understood. Secondly, it is a placebo effect that can be studied in healthy volunteers in a non-clinical setting, which facilitates the experimental process and avoids the risks and challenges in experimenting on a population with an illness or disorder.

The difficulty in studying pain, however, is the same difficulty faced by clinicians; it is difficult to judge the physical pain of another person. The most relied-upon method to date is self-rating scales. In clinical settings these ratings scales come in a variety of forms, such as drawings of faces with varying levels of discomfort. In experimental settings the most common scale is the visual analog scale, consisting of a simple horizontal line. The scale is sometimes 100mm in length, and the ends are usually marked by words, such as "no pain at all" and "extreme pain." Typically the line is not divided up by tick marks, numbers, or other markers (Price, McGrath, Rafii, & Buckingham, 1983).

Since healthy volunteers are used for experimental purposes, such as the assessment of analgesic products and pain-management techniques, researchers must be capable of inducing pain during a study. There are a number of validated methods for experimental pain. One of these methods is electrical stimulation (electric shocks). These shocks are commonly delivered either to intact skin, purposefully damaged skin, or the tooth pulp. The advantage to this method is that shocks are brief and transient, so that a number of shocks, at different intensities, can be delivered over the course of an experiment. Electric shocks do have some disadvantages. The most important of these, argued by

some researchers, is that this type of pain may not physiologically mimic natural pain (Handwerker & Kobal, 1993), (Staahl & Drewes, 2004), (Bromm, 1985). Another challenge of electric shock pain is that the subjective intensity of the pain may not be entirely linear with increasing voltage; as voltage rises, a person's ability to discriminate between different intensities decreases (B. Jones, Planas, & Anuza, 1982). NSAIDS are not believed to have any effect on electric shock pain, although opioids may (Parry, 1979).

Another common method is the 'cold pressor' test. The cold pressor test is considered to be a good model of chronic pain, and is quite simple in principle. The experimental subject immerses their hand in cold water for a short period of time. Researchers study the amount of time the subject is able to keep their hand in the water and/or self-ratings of the pain during that time. There is relatively little standardization in the details of the methodology across studies; the water temperature is generally between 1 and 7 degrees Celsius and the length of the test is generally between 1 and 5 minutes (Mitchell, MacDonald, & Brodie, 2004). It is preferable for the water to be circulated during the test to provide constant water temperature, but this is not always done in practice.

Other methods of experimental pain induction include needles, mechanical pressure, heat, and focused laser beams. All of these methods are frequently used, and there is not one single method that enjoys a monopoly. The methods are analogous to different types of natural pain, with shock pain belonging to the acute pain categorized as 'first pain' and cold pressor pain being the more chronic 'second pain,' which are represented differently neurologically (Ploner, Gross, Timmermann, & Schnitzler, 2002). In the experiments below, shock pain and cold pressor pain are used.

Price-Quality Assumption

Traditional models of economics posit that consumer utility from a good or service is determined accurately by each individual consumer. The consumer calculates how much utility they will receive from a T-shirt, apple, or scuba diving class, and then accepts the transaction if the seller price is below their reservation price. In this model the demand for a product should be independent of the actual utility given by the product, and higher price should be associated with lower demand. In contradiction to theory, though, business and economic researchers are aware of anomalies in the typical shape of demand curves. Specifically, higher price is sometimes associated with *higher* demand, not lower.

Research over the past several decades has examined this phenomenon and determined one major reason is that individuals sometimes use price information as a proxy for quality. In other words, price information may be used as a heuristic by which people infer the relative merit of a product or service, be it familiar or unfamiliar (Rao, 1989). Considerable research has established that people quite often perceive price-quality correlations across a wide range of products. Quite frequently the perceived price-quality assumption is actually not objectively accurate. In many different arenas of consumer products, no correlation (or even a weak negative correlation) has been found to exist,

although price and quality move together more often in non-durable goods categories (Riesz, 1979) (Wolinsky, 1983) (Lichtenstein, 1989).

This is a phenomenon with which many readers may be intuitively familiar, and yet there are a number of potential reasons for this price-quality assumption. One cause may be the information asymmetry inherent in the consumer-seller relationship (Akerlof, 1970). Consumers are unable to have as much information about a product as does the maker/seller of that product. Despite this disadvantage, consumers are still tasked with the need to sift through their many choices and decide upon the best or most appropriate purchase for their needs. This is an incredibly difficult task. Because many of the important qualities of a product may not be obvious (for instance, longevity, the quality of internal parts, customer service) companies have the need to “signal” quality in a visible way.

The situation is reminiscent of quality signals in nature. When choosing a mate, naturally an animal (in particular a female) desires a mate who will provide the best fitness to their offspring, in order to protect their own genetic contribution, but quickly sizing up the genetic fitness of a potential mate is not easy. Biologists and zoologists believe that apparent handicaps (heavy, bright peacock feathers that use precious energy to maintain, the building of ornate structures by bower birds who could otherwise be finding food, etc.) may function as fitness signals since only a very healthy, skilled animal could maintain these features or behaviors (Iwasa, 1991).

Similarly, a high price *should* be a handicap for a product’s sales in the traditional model of economics. The fact that an expensive product is so pricey and still on the shelves may signal to consumers that it must warrant that price and must have some significant advantage over less expensive products. Higher prices may also serve as a signal that more expensive materials or processes went into the manufacturing of the item.

Of course, in nature as in consumer products, not all signals are “honest” in reporting their quality. A \$1000 luxury purse may not genuinely be of much higher leather quality or design than a \$100 bag. (On the other hand, the consumer walking around with the expensive purse may be doing her own value signaling!). The high price may merely reflect high margins on the part of the retailer/manufacturer, or in other cases may reflect high advertising and marketing costs. It may be argued that rationally, intense advertising campaigns should decrease a consumer’s expectation for a product as it relates to price, since one can logically infer that at least some of that its price must be paying for marketing. However this effect does not generally seem to be the case, and billions of dollars continue to pour into advertising for luxury and midrange products.

Instead, advertising and marketing have the power to enhance consumer perceptions, perhaps creating in this way self-fulfilling prophecies for price-quality assumptions. For instance, a recent study has shown that increasing the stated price of a wine increased not only subjective reports of its taste, but also fMRI activity in the medial orbitofrontal cortex, which is believed to be related to experienced pleasantness (Plassmann, O’Doherty, Shiv, & Rangel, 2008). And if price can increase perceived utility in this

way, then in reality it does have value beyond that discovered in objective, price-blinded quality studies. Especially relevant to the current research, if price can increase expected value, then in the case of medical products, it may be able to modify not merely perception, but the *actual product performance* via the placebo response.

There has previously been very little research aimed at directly testing the hypothesis discussed above, that prices can impact the direct effect of a medical product by modifying the placebo effect. One study by my colleagues, which used the energy drink SoBe, found that a price difference could impact the placebo cognitive benefits of the drink (Shiv, 2005). Another thought-provoking paper found that the price of a drug could predict effects on health-related quality of life; the higher the average wholesale price, the better the quality of life, regardless of what specific condition it was for. The researchers were unable to determine the cause of this strange relationship but were surprised at its strength. One possible explanation, according to the authors, was that pharmaceutical companies might price products in accordance with their benefits on health-related quality of life. Another possible argument would be that it might have to do with the research and development costs of the pharmaceutical company, and that higher R&D costs might lead to both the higher prices as well as apparently superior efficacy. However, there are multiple problems with either explanation, since pricing is a complex decision based in a dynamic marketplace that cannot be made directly based on R&D costs or clinical trial efficacy (Murawski, 2003). On the other hand, this research could potentially support the hypothesis presented here, that price may have a direct effect on medical outcomes.

It is noteworthy to point out that price is not the only important signal of quality. Another is the country of origin of a product. Because global trade is a vitally important issue for all economies, there is a need to understand consumer attitudes towards foreign and domestic products. In particular, a large body of research has found that consumers in developed countries display a preference for domestic products. “Made in USA” (or other home country) may serve as a quality cue and/or as a ‘low-risk’ cue. The concept of consumer ethnocentrism comes into play when consumers attach additional value and quality judgments to domestic products (Shimp, 1987). Research on consumer ethnocentrism has suggested that foreign manufactures might want to downplay their foreign origin (Watson, 2000), although this is not always possible. In the United States, American-made products are sometimes considered preferable both because of the economic benefits to the country and because of perceived superior quality in certain categories.

In contrast to this there are countries whose products consumers actively avoid. Over the past few years and particularly in 2007, many Americans, including the media, have wondered if the United States should ban food and drugs from China (Tonelson, 2007). This followed scandals involving tainted pet food (which caused a number of feline deaths), toothpaste, and lead-painted children’s toys (Barboza, 2007), (Lipton, 2007), (Bogdanich, 2007). Because of these starkly contrasting opinions of products from different countries, and in particular the United States versus China, consumer ethnocentrism has the potential to be a relevant issue in international trade and a source

of unexpected economic perturbations. Accordingly, the hypothesis is that: consumers would place greater value and quality signals on an American product, and that this effect might also modify placebo responses.

Price and country of origin are not the objectively best ways to make an assessment of quality. Because it is not possible for the average consumer to consult an informative and unbiased source of information like Consumer Reports for every minor purchasing decision, heuristics and rules of thumb are useful ways to help people make decisions. Even if these heuristics fail us at times, they at least allow us to decide upon something quickly and accurately on average. It is only those rare instances where the failure of our heuristics lead to some significant unwanted outcome that we must re-examine what rules we rely upon for our expectations, perceptions, and decisions. In the case of medical therapies, unwanted outcomes would include poor choices of the best treatment as well as reduced efficacy of a treatment.

Laboratory Experiment 1

Veladone Experiment Methods

To design a laboratory experiment to determine if marketing factors could modulate placebo effects, it was important to take great care in creating the right atmosphere and environment, and to keep procedures very consistent across subjects. For the initial laboratory experiment, it was decided to examine both a difference in price as well as a difference in country of origin, on the efficacy of a placebo analgesic.

Subjects and Recruitment

82 subjects participated in the experiment. Potential candidates were excluded if they had a history of cardiac problems, epilepsy, diabetes, or were pregnant. Participants were between the ages of 18 and 65 (mean age was 30 ± 11.84) and taking no pain medication at the time of the experiment. Participants were not selected on the basis of gender, and 31 of the 82 subjects were male.

The subjects were recruited with an online advertisement explaining that they would receive moderate electric shocks to their wrist and fill out a questionnaire of their past painful experiences. The experiment was described as a study of how an individual's past history of painful experiences related to their current response to pain-reducing medication and painful stimuli. However, there was no active selection based upon subjects' past history of pain.

Procedure

There were two conditions in this study, price and country of origin. Each of the two conditions contained two levels; price was either \$2.50 per pill, or discounted from \$2.50 to \$.10 per pill. Country of origin was either American or Chinese. This information was presented to the subjects both verbally and in written form in a brochure about a medication, which was invented for the experiment and actually a placebo. The brochures also contained other information about the purported medication, Veladone Rx,

such as its indication (moderate pain, such as after dental surgery), the fact that it worked quickly, and potential side effects (such as nausea and dizziness). Using an invented drug avoided confounds based upon a subject's pre-existing relationship with a medication. Four brochures were created which were identical except for the price and country information. Participants were randomly assigned to one of the four groups. The experiment room was carefully set up to be moderately medical in character, with such props as biology books on shelves, a lab coat for the experimenter, and a blood pressure test.

Because placebo effects are so sensitive to the opinions and knowledge of a medical practitioner, the experimenter was blinded by use of a confederate. Participants were familiarized with the study procedure by the experimenter, who was introduced as a graduate student in pharmacology. They then spoke with a "representative from the pharmaceutical company," who gave them the brochure about the medication as well as a promotional pen with the drug name, and answered any questions they had about the drug. The experimenter left the room during this time to maintain blindness. The pill was explained by the confederate to be a newly-FDA approved, effective analgesic pill that might modify their pain experience. It was described to cost either \$2.50 per dose or to be discounted from \$2.50 to \$0.10, and to have been manufactured either in North Carolina or in China. Subjects were randomly assigned to one of the 4 groups (high price America, high price China, low price America, or low price China). The assistant confirmed that subjects had attended to the target information by administering a short manipulation check quiz on information contained in the brochure, including the target information of price and country. If a subject made an error on the answers to the two pieces of target information, they were corrected before moving on. The confederate then left and the experimenter returned.

After subjects were familiarized with the procedure and medication, they were introduced to the stimuli, a series of 100ms electric shocks applied to the volar surface of the right wrist using an SD9 stimulator (Grass-Telefactor, West Warwick, Rhode Island, USA). The area on the wrist was first cleaned with alcohol and a conductivity-increasing gel was used. To calibrate stimuli intensity to the appropriate range for each subject, subjects' maximum tolerance was determined to be the voltage they rated as an 8 out of 10 on a scale ranging from "no pain at all" to "intense pain." The experimenter started at 10 volts, which was imperceptible to most subjects, and increased voltage intensity until participants verbally rated that pain as an '8'. This was the highest intensity subjects received at any point during the experiment. The calibration and shock methodology was modified from that used in Berns et al 2006 (Berns et al., 2006).

Subjects next received a series of shocks, which were all possible shocks between 10 volts and their calibrated maximum tolerance in 2.5- V increments. Therefore the total number of shocks depended on subjects' calibration and never exceeded the calibrated maximum; mean number of shocks per round was 20.72, and a number of these tended to be below the subject's pain perception threshold. Subjects rated the perceived intensity of the shocks on a computerized visual analog scale anchored by the words "no pain at all" and "the worst pain imaginable."

This first round of stimuli was followed by subjects' receiving the placebo, which was a small red pill suggestive of commercial over-the-counter pain relievers. After a waiting period of 15 minutes to give the medication time to 'take effect,' a second round of shocks commenced analogous to the first round. During this waiting period, the wrist electrode was removed, but its exact location was drawn on the participant's arm so that it could be replaced in the same position. At the conclusion of this waiting period, the VAS rating procedure was repeated. The random order of voltages in the first round was precisely replicated in the second round, such that if the first shock of the first round was 20 volts, the first shock of the second round was also 20 volts.

At the end of this session, subjects completed a questionnaire regarding their attitude towards, and history of, painful experiences. Then subjects were thoroughly debriefed regarding the true purpose of the study.

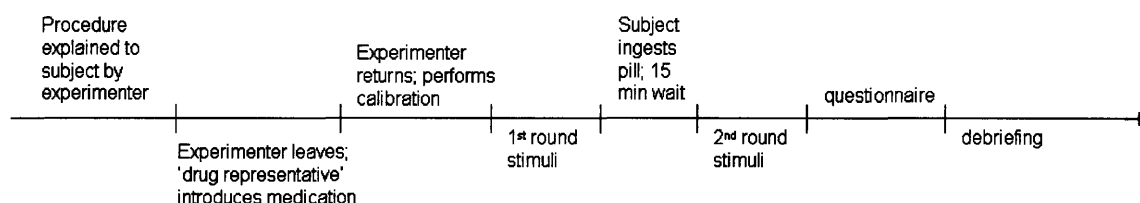


Figure 1: The experimental timeline of the Veladone experiment.

Veladone Experiment Results

The main unit of analysis in the analysis of the Veladone data was the difference scores for each participant- the change at each intensity level between the first round of shocks and the second round. Studying only the between-condition difference of the difference scores eliminated irrelevant sources of variance from consideration. (This is important because the difference between round 1 and round 2 is not uniquely a placebo effect, as additional factors such as demand effects and habituation could be involved. The difference between conditions, however, will only be affected by the price or country manipulation). The VAS ratings were simply converted to a 100-point scale, and the second round was subtracted from the first round.

Mixed-Effects Model

A linear mixed-effects model was fit with subjects as a random factor and all other variables as fixed effects. Neither age nor gender were found to be significant factors and so were excluded from subsequent analyses. The voltage of each difference score was entered into the regression to control for the physiologic differences in pain sensation at different voltages; this factor was significant, as predicted. Overall, 73% of subjects rated the shocks to be on average less painful during the second round. However the

focus was not on this reduction but rather if manipulation of price and country of origin would influence the placebo response.

As is expected for physiologic reasons (B. Jones, Planas, M., Anuza, T., 1982), the Voltage level of each shock significantly affected the difference score ratings ($p < .0001$). The Price manipulation was also significant, as expected, and this is further discussed below. The Country manipulation was significant, but in an unexpected direction, and as discussed in a later section, this is actually due to the significant interaction with Ethnicity (Asian versus Non-Asian). The factor “Pain Day” in the table relates to the subject reporting having had pain on the day of the experiment unrelated to the electrical shocks, and is also further discussed below.

	Value	DF	t-value	p-value
Intercept	-13.41	1040	-1.21	.228
Voltage	1.90	1040	5.34	.000
Price(Low)	-25.00	65	-3.22	.002
Country(China)	41.84	65	2.84	.006
Ethnicity(Non-Asian)	28.27	65	2.79	.007
Pain Day(pain-free)	-8.70	65	-1.09	.282
Price(Low)*Country(China)	-9.45	65	-1.03	.308
Country(China)*Ethnicity(Non-Asian)	-36.67	65	-2.80	.007
Price(Low)*Recent pain (no pain)	35.12	65	3.65	.001
Country(China)*Recent pain (yes pain)	-4.92	65	-0.51	.612

Table 1: The results of the mixed-model regression show the significance of Price, Country, Ethnicity, Voltage, and the interactions between Country and Ethnicity and Pain Day and Price. Note that this analysis does not include those 8 subjects who due to a clerical error did not respond to the ‘recent pain’ question on the questionnaire.

Price Manipulation

A chi-square test showed a significant difference between the number of people experiencing an overall reduction in pain reported, versus an overall increase in pain reported, between rounds. In the non-discounted condition, 78.1% of the participants experienced a mean pain reduction after taking the pill, versus 56.1% in the low-price (discounted) condition, a significant difference per 2-tailed chi-square-analysis $\chi^2(1, N=77) = 6.0, p < .05$). Because some research suggest that stronger pain may be associated with stronger placebo responses (Harrington, 1999), the most painful 50% of shocks was also tested, and the same pattern was found; 80.4% of high-price condition participants experienced mean pain-reduction versus 53.7% in the low-price condition. Again, 2-tailed chi-square-analysis is significant $\chi^2(1, N=78) = 5.7, p < .05$).

Likewise, when considering the data for each stimulus intensity, 26 out of the 29 intensities showed greater pain reduction was greater for the high-priced than the low price pill (a sign test of these differences is significant at the $p<.001$ level).

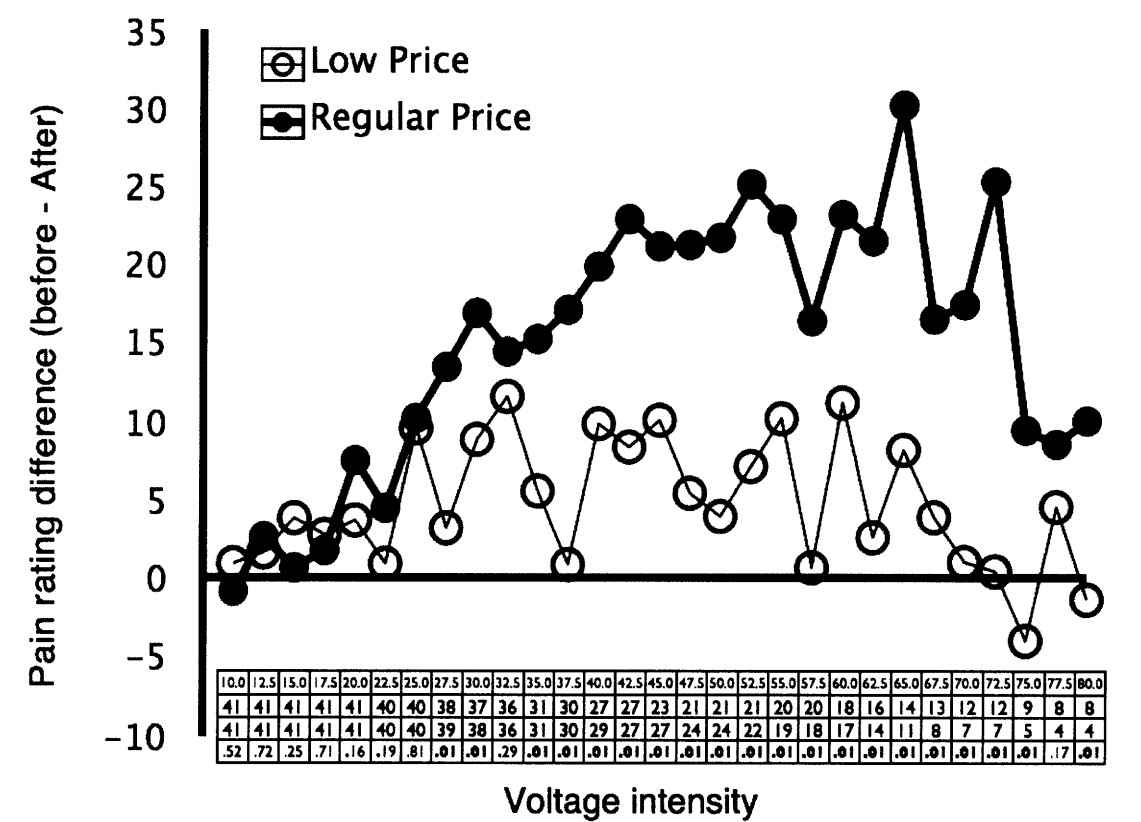


Figure 2: Mean difference in pain ratings, after vs. before placebo, by voltage intensity. The table depicts the intensity of the shocks (top row), the number of observations in the high price (2nd row) and low price (3rd row) conditions, and the significance level of each difference (bottom row).

Country Manipulation

Contrary to the original hypothesis, the America condition was not superior the China condition. In fact, overall the China condition produced greater analgesia. However, when this is broken up by subject’s ethnicity, a very different picture emerges. An interaction was found between country of origin and the ethnicity of the subject. Ethnicity was taken to be a very rough measure of Asian (including both Asian-American and Asian) versus non-Asian ethnic background. The average mean difference score for Asians in the United States condition was -5.8, indicating that their pain ratings were actually higher in the second round after receiving the placebo, whereas in the China condition the average mean difference score was 22.17. This is a significant difference, (clustered t-test $p<.001$). Among Non-Asians, however, there was no difference for the country factor (M-United States 9.62, M-China 13.16, clustered t-test $p=.352$).

Effect of country-of-origin & Ethnicity

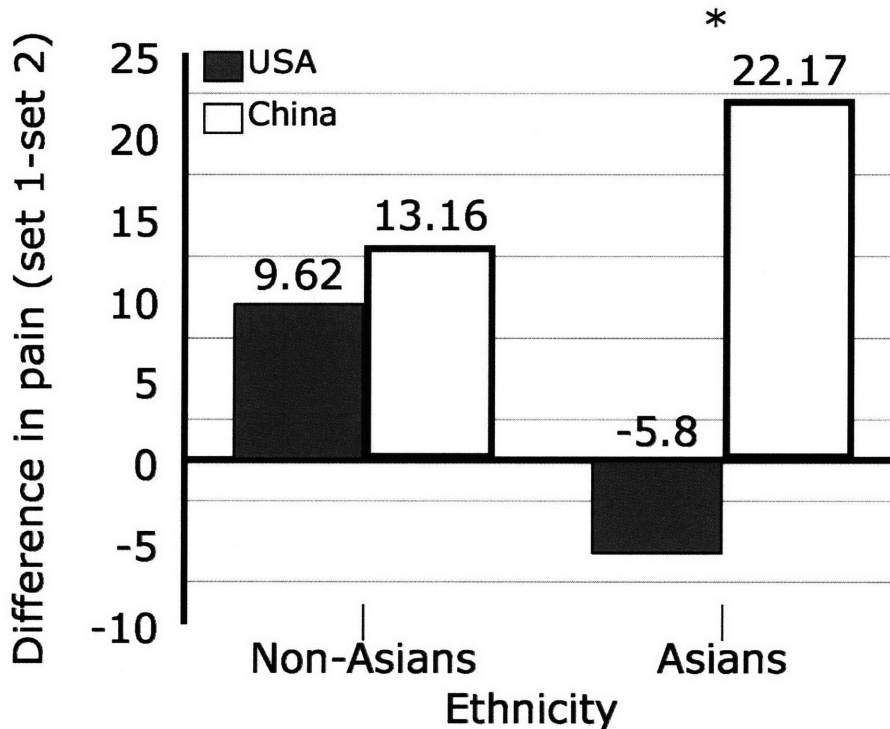


Figure 3: Country of origin has no effect on pain for non-Asians, but the China condition is significantly better than the American condition among Asians.

Price interacts with subject's other pain experiences

In the questionnaire administered after the second round of stimuli, participants were asked if they had experienced pain (even mild pain such as a headache or a sore muscle) during the day of testing, before the experiment. Participants' response to this "recent pain" question significantly interacted with the price factor, such that participants experiencing recent pain responded much more strongly to the price manipulation and reacted more negatively to the discounted treatment (see figure). The explanation of this effect will rely on future research, although one hypothesis is that these individuals experiencing recent pain also had more salient, recent experience with taking analgesic medications. Subjects who report experiencing pain other than the experimental procedure the day of the experiment, or the month prior to the experiment, show a significantly different response to the two price levels ($p < .05$) than do subjects reporting no pain in this time frame ($p = .237$). This interaction is significant, $p < .001$. Subject's self-report of painful experiences during their lifetime, however, does not interact with response to the Price factor.

There are several interesting explanations for these results. It may be that individuals who have experienced recent pain also have more experience taking analgesic medications, and have been convinced of a price-efficacy correlation in the real world. It is also possible that part of this effect is mediated through another factor, that of perceived pain tolerance. Subjects were asked to indicate how their pain tolerance compared with other individuals, and we found a significant correlation between experiencing recent pain and considering oneself to have an above-average pain tolerance ($r=.399$, $p<.001$). This may imply that experiencing pain can influence an individual to judge themselves good at coping with pain. Interestingly, this perceived pain tolerance is uncorrelated with objectively measured pain tolerance (the calibration procedure of the experiment), ($r=.068$, $p=.543$). An individual's perceived pain tolerance may affect placebo effects via its effect on the affective characteristics of pain for that person and their emotional state, which are known to moderate placebo responses (Zubieta, Yau, Scott, & Stohler, 2006).

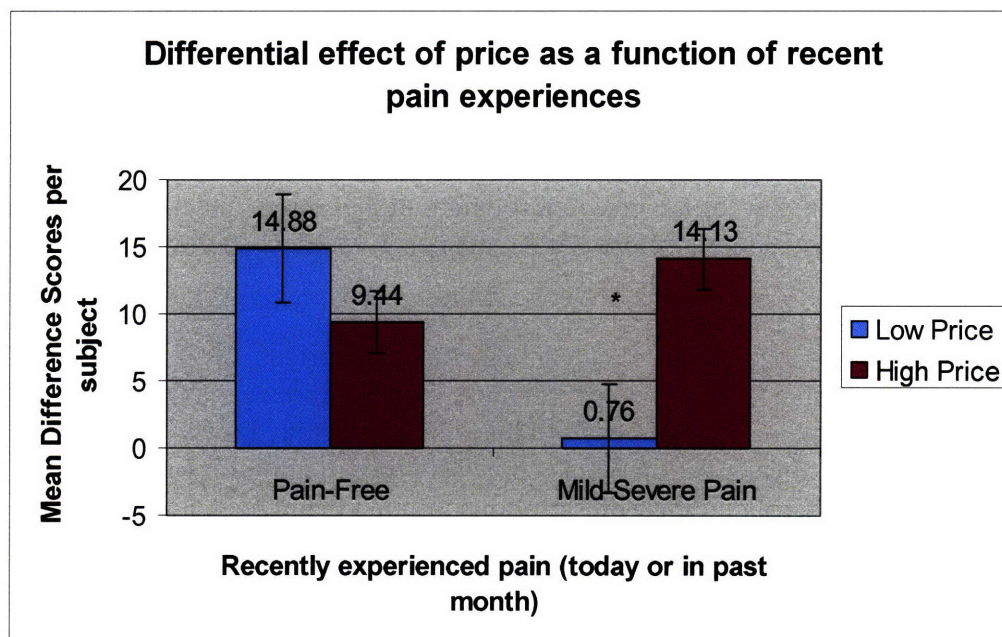


Figure 4: Among people experiencing no recent pain, there is no clear effect of the discount manipulation. Among people experiencing pain the day or month of the experiment, the undiscounted pill is significantly better than the discounted version.

Veladone Experiment Discussion

The results of the Veladone experiment, particularly the Price manipulation, are striking. The effectiveness of the price manipulation is particularly thought-provoking given that it was relatively subtle and naturalistic; Price was merely one piece of information out of many provided to the subjects, and it was not directly related to drug effectiveness as, say, mode of action would be. Many studies that aim to invoke placebo responses rely on a combination of strong verbal suggestion (“this is a powerful analgesic”) and direct experience of the placebo’s effectiveness (i.e. by turning down the intensity of the stimuli

to make it appear the placebo is working) (Petrovic, 2002). Yet the current results suggest that placebo effects may be manipulated by factors that are considerably more indirect and that are naturally found in consumer's experience with medical products. In addition, there are ways in which the expectancy manipulation used here is considerably weaker and than the marketing and pricing issues that typically come into play in consumers' lives. Not only were our subjects merely told about the price of the drug, as opposed to actually paying for it, but they did not experience the massive amount of advertising that often accompanies pharmaceuticals in the real world.

It is worth highlighting that it is likely not the absolute price of the drug behind the reduction in efficacy, but rather the impact of the discount on subjects' evaluations of the medication. In the absence of an explicit discount, moderately low prices will probably not have a large negative effect simply because the average consumer (and physician, for that matter (Allan, Lexchin, & Wiebe, 2007)) has only a vague idea of appropriate prices for medications. However, while absolute value evaluations are difficult to make, the relative evaluation of normal price versus discount prices is much more obvious, and it is this relative evaluation that puts the discounted product in a negative light (Ariely, 2003).

One might wonder also what the effect would be when the consumer is provided with a coherent and reasonable reason for a certain price discount; would this reduce the negative effect of discounting? This remains an open question, although the results of the past study that used SoBe suggest that this would not counteract the nocebo effect. In that study a logical explanation for the discount (being told that it was due to being an institutional bulk purchase) did not protect against the negative effect of the discount (Shiv, 2005).

Because relative discounts may be more relevant than absolute prices, the implication is not that pharmaceuticals should be priced exorbitantly high to produce maximal effects, but rather that high baseline prices coupled with discount prices may lead to some loss of efficacy. It is worrisome to consider that this is precisely the situation for low-income and elderly individuals who obtain their prescriptions through the patient assistance programs run by most major drug companies for people without health insurance and low income.

The fact that the country of origin manipulation did not fit the hypothesis is interesting. The lack of any effect among non-Asians may relate to the lack of any explicit relative evaluation for this condition. Unlike in the discount condition, where attention was drawn to the difference between the full price and discount, in the China condition there was no mention of, say, a move to outsource production from the United States. Another reason for the lack of difference may simply be that people did not have a uniformly negative quality evaluation of products from China, as this was before the string of China-related quality control scandals. An informal survey of undergraduates at the time corroborated that idea; they said that they would not have any problem with medicine from China but might have some concerns if it were from a country less well known for imports, such as Thailand or the Philippines. In fact, subjects showed great variability in their opinion of Chinese drugs, and much of this opinion was not negative. Some

mentioned, for instance, that they had to be the same as American drugs since it was FDA approved. Other said that since traditional Chinese medication was effective, this product would be too. Another issue might be that even when consumers place more value on a product from the United States, it does not necessarily mean that they believe it to be of higher quality (the greater value could come in some other form, such as supporting American jobs).

Laboratory Experiment 2

Significance of Brand Name

Brand as cultural information

Brand names are cultural information and in essence a fundamental part of the ritual surrounding a modern medical object (Greenslit, 2007). Brands touch upon quality signaling, issues of personal identity and choice, nostalgia, and group affiliation. It is also known that brand name is able to strongly affect people's perception. One well-known investigation of the role of brand name on perception involved Coca-cola and Pepsi-cola, for which people regularly express a preference irrespective of their very similar composition. Subjective taste tests of unlabeled Coke and Pepsi showed equal preference for each beverage, but a taste test with the Coke label showed a bias for Coke in the population studied. The neural correlates of this brand-information-modified sensory perception were then demonstrated with fMRI. While in the scanner, subjects drank Coke or Pepsi while possessing or not knowledge of which brand it was, and brand knowledge (at least of Coke) was associated with neural response in the dorsolateral prefrontal cortex, separate from the sensory perception of the experience in the ventromedial prefrontal cortex (McClure et al., 2004). Accordingly, just as other informational cues and rituals are important in the placebo response, it seems quite possible that brand would be too (Kaptchuk, 2002).

However generic products are of increasing importance, especially in the arena of pharmaceuticals. The percentage of prescriptions that are generic in the United States has been growing over the past decade to the 2007 rate of 67.3% of all prescriptions (Koroneos, 2008). When it comes to generic medicines, however, quality may be questioned.

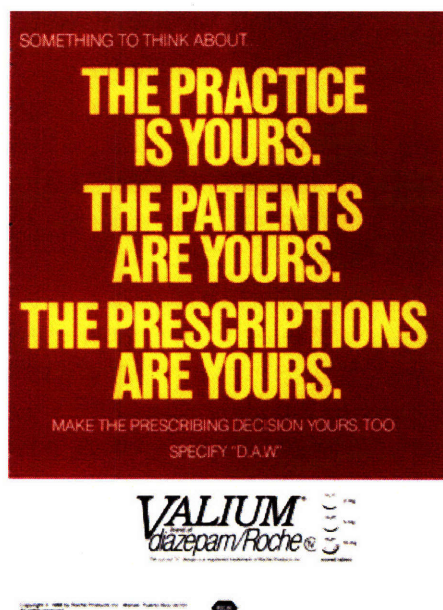
The FDA states that generic drugs are exactly equivalent to their brand-name counterparts. Specifically, the FDA states that a generic drug "is a copy that is the same as a brand-name drug in dosage, safety, strength, how it is taken, quality, performance, and intended use (FDA, 2008)." Despite this official position, physicians and patients alike display uncertainty about the equivalence of generic and branded medications (Meredith, 2003), (Pereira et al., 2005), (Hassali, Stewart, & Kong, 2008), (Banahan & Kolassa, 1997), (Kjoenniksen, Lindbaek, & Granas, 2006), (Kirking, 1990), (Himmel et al., 2005)

Trust in generic medications is known to be less than absolute. For instance, documents exist to instruct pharmacists in how to discuss the issue with patients and educate them on the therapeutic equivalence of generic medications, when the pharmacist but not the

patient assumes equivalence (USPharmacist, 2007). And for some conditions, such as epilepsy, generics are not recommended even by their official organizations (Epilepsy.Foundation, 2008). There are even reported cases of such intense distrust of generic medications that it results in “somatic” disorders, such as the case study of a woman believed herself allergic to all generic medications and became acutely itchy upon taking any kind of generic medicine (Brennan & Lee, 2004). However, low-to-moderate distrust of generic medications, as a function of its pervasive nature, seems even more worrisome.

One ethnographic study in France found that a number of individuals spontaneously expressed their ambivalence and uncertainty, and even suspiciousness, towards generic medications. People expressed disbelief that generics and brand-names were *really* identical, even if they *knew* they were and had been taught by the pharmacist or doctor that they were identical. One man was quoted as saying, “it’s maybe the same molecule but it’s less... strong!”(Sarradon-Eck, Blanc, & Faure, 2007).

The belief that a quality difference exists between brands and generics may also be promoted, logically enough, by brand-name pharmaceutical companies, such as in the advertisement below, or as Eli Lilly did on their website after the 2000 introduction of generic fluoxetine (Greenslit, 2007).



Graphic 1: This Valium ad encourages doctors to demand branded medications.

This thesis does not take a position on whether or not there are truly no biologic differences, in any circumstances, between branded and generic medications. The truth about generic drugs is likely to be more nuanced, such that certain medications are affected by differences in binding agents or particle sizes, resulting in therapeutic differences, while in general generics are very acceptable substitutes. What is relevant for this document, however, is the belief that generics may be inferior, even in situations

where no relevant bioavailability or other differences exist (Meyer, 2001) because lack of trust in a generic product might run the risk of reducing the placebo response to that product. Actually, this issue of reducing the strength of the placebo effect is relevant both in situations where the generic is factually equivalent as well as when it is not, although in the latter situation any placebo benefits might well be outweighed. Therefore the rest of this discussion will focus on situations where the two formulations are therapeutically equivalent from a biological point of view.

Ambivalence towards generic medications by patient and physician comes in differing degrees. Some people may hold explicit negative views towards all or specific generic medications. However, weaker, implicitly held beliefs of moderate doubt may be very relevant as well.

Surveys on Attitudes towards generic medications

A survey was conducted on the MIT campus with 93 individuals (mean age 28.42 ± 11.92 , 50 female). In this survey, respondents evinced moderate doubt in the idea that generics and brand-name drugs are entirely equivalent. Given the questions, “are generic drugs as effective as brand-names” and “are generic drugs made to the same standards as brand names,” the average participant response was a 5.7 and 5.3 respectively, on a 7-point scale. While this difference is significantly different than a response of 4, or entirely ambiguous ($t(92)=14.75$, $p<.001$; $t(92)=10.26$, $p<.001$), it is also significantly different from 7, or complete confidence ($t(92)=11.29$, $p<.001$; $t(92)=13.40$, $p<.001$).

Because attitudes towards generic medications are particularly relevant among geriatric populations, a similar survey was conducted at an AARP event. 56 responses were collected, age 63.2 ± 8.77 . 41 were female, 8 male, and 7 did not indicate gender. Although there was high New England/Northeast representation, nearly 50 zip codes were represented. The respondents took an average of 3.45 ± 2.54 prescription medications each, however it should be noted that this does not represent population values as recruitment was biased towards individuals who took at least one medication. (Only 4 respondents took no medications). Respondents indicated how many of their medications were generic. 44.7% of prescription medication were generic, but there was considerable variability (standard deviation is ± 34.8 percentage points). 25% of people take took at least one generic medication, 21% said 50% of their medications are generic, and 15% responded that 100% of their medications were generic. In the AARP group, the average response to the question about generic drugs being as effective as brand-name drugs was 4.91 (again, on a 7-point scale), and the average response to if generic drugs are made to the same standards as brand-name drugs was 4.82. Interestingly, this means that the overall responses in the AARP group showed significantly more distrust of generic medications than in the younger group. (For “effective,” $p<.001$; for “standards,” $p=.052$).

Doubt in generic medications goes along with the intense importance of medicine. Given that medications are intimately tied to both the duration of and quality of a person’s life, doubt in a generic medication may be likened to Pascal’s wager, the 17th-century French philosopher who argued that a person’s best bet in life is to believe in god even if the

odds of his existence are exceedingly small. The argument goes that the reward for being correct (heaven) is infinitely better than the penalty for being wrong (hell), and thus any doubt whatsoever must lead to acting upon that doubt. Similar thought processes seem to be in play regarding generic medications. Although a person may generally believe that generics are equivalent, when the stakes are high (life), taking the generic is simply not worth the risk. This may be an entirely reasonable response, and it indicates quite clearly that doubt in generic drugs is rampant.

In fact, this is the type of response received in the questionnaire. Among those 27 individuals who did say they believed generics and brands were entirely equivalent (an answer of '7'), all said that they would take a generic medication to treat a cold, but fully 52.2% said that they would not choose a generic medication to treat cancer. The same results were found with other serious versus nonserious conditions. Across all the respondents for 12 health conditions that ranged in seriousness, people said they would take a generic for an average of 6 of them (50%). But, for the 6 conditions classified as "serious," people would take a generic for an average of 1.8 of them (30%). Such a response indicates that even people who logically believe in the equivalence of generics and brands would change their outward behavior and choose the brand. If outward behavior is changed, then it seems likely that there are reasonable seeds of doubt in the person's mind that could influence the expectations and beliefs that are the core of the placebo response.

Because of these trust issues revolving around generic medications, research is necessary to determine if these beliefs can be responsible for negative health outcomes by modulating placebo effects. On the AARP survey, respondents were asked about experiences switching from the generic to brand-name version of a drug or vice versa. 33% of people indicated that had at least once switched from a generic drug to the equivalent brand-name drug, and that on a scale of 1-7 in terms of being more satisfied with the new (brand) drug, they averaged 5. On the other hand, 82.7% of people said that they ever switched from a branded medication to a generic, and the average satisfaction rating was only 4.09. This means that people were significantly less satisfied with a medication change when they changed *to* a generic instead of *from* a generic ($p < .05$).

Qualitative Interviews

Nine qualitative phone interviews were conducted with individuals who responded to an online advertisement for people who had experience with both brand name and generic drugs, in order to learn about the kind of language that people use about brands and generics.

A number of respondents with experience with both the generic and brand name of a drug believed the two versions to have been equally effective for them. Interestingly, even if a particular generic seemed to work, this did not mean that generic had the benefit of the doubt. One 61 year old man who had been forced to switch from a branded to a generic medication expressed his belief that generics could be, but were not necessarily, equal to branded medications in the statement, "I took the precaution of calling their pharmacists [to] give me the short course on generic versus brand name. [There are] different grades

of generics drugs, you know, and their particular pharmacy only handles the higher grade that's passed FDA scrutiny."

This caution relating to generic medication was a recurring theme. Several people said that they asked their doctor or pharmacist if taking the generic was okay. One 40-year old woman discussed the fact that she usually takes generics, but that for her son she buys only branded medications (OTC in this case), saying "I won't go generic with him." Another woman stated that "I have complete faith in generics" but later mentioned that "maybe the integrity of [brand-names] are superior."

Several respondents mentioned more active feelings against generics. One interviewee talked about her husband's belief that generics will not work as well, which she attributed to not being adequately informed on the subject. With regards to generic antidepressants, her husband blamed any behavior change on the medication switch. Another, 60-year old woman stated that she "feel[s] bias towards generics without really having facts." She also stated that her endocrinologist had informed her that generics have worse quality control. She discussed 3 medications that, for insurance reasons, she had switched from the branded to generic form. For two of the medications, she stated that the generic did not work as well as the branded version (and for one of these, the relevant professional association has stated that generics are equivalent(AACE, 2008)), while the third medication seemed to have the same efficacy in generic form.

Patient Education

Education of physicians and patients is sometimes discussed as the solution to inaccurate beliefs about generic medications. In fact, survey respondents seemed to desire more education. When asked, if "I know enough information about medicines to make a good decision between brand-name and generic drugs" only 14.5% of the AARP group and 10.8% of the younger group "strongly agreed," and the average response was 4.5 and 4, respectively. This confusion was also expressed by the fact that while the respondents indicated a moderate distrust of generic medications, at the same time, they strongly disagreed with the statement, "Price generally reflects the quality of a medicine, such that a more expensive medicine is likely more effective than a cheap medicine," answering on average 2.5 out of 7. People also disagreed to some extent to "I try to buy the brand-name version of a medicine whenever possible," giving it 3.4 out of 7.

However, education cannot be considered a panacea because of the fact that rationally-held beliefs may not override the power of emotional impulses when it comes to attitudes towards generic drugs. Education may lead people to *know* that a generic is equivalent to a branded medication, but it has a difficult task in eliminating all doubt.

It is also important not to prematurely believe that an educational process is complete. It may be possible, after a discussion with an informed physician or pharmacist, to successfully induce a patient to choose the generic medication. However, this choice, made under some degree of pressure (however well-intended), can not be evidence that the patient truly believes in the generic product.

Implication of distrust of generics

The debate over generic drugs has serious consequences. Prices for generic drugs average 30-80% less than brands, and the savings to the health care system of using generic prescription medications are enormous. In one study, full use of available generic drugs would have saved \$5.9 billion annually in the United States (Haas, Phillips, Gerstenberger, & Seger, 2005). As a result, it is clear that there are real reasons to promote generic drug prescribing. And yet, if this is successful, the lack of trust displayed in these products could have real implications for the placebo component of their effects and potentially, real health implications.

To date, the only (known) published paper that considered the role of brand name on the efficacy of medical products is a 1981 paper by Branthwaite and Cooper in the British Medical Journal. In this paper, 835 women were given a painkiller, which was either placebo or active aspirin, and was either a well-known branded or generic form. Over a 2-week period, subjects were instructed to use the tablets to treat any headache they developed, and the researchers analyzed self-report of the efficacy of the medication. This research found that more headache relief was provided by the brand-name than generic versions. However, this research was limited in that it was relatively uncontrolled. For instance, in this study subjects in the branded conditions reported more headaches than subjects in the unbranded conditions, so the brand manipulation may have had confounding effects on the decision to take a medication, rather than solely the medication's effect (Branthwaite & Cooper, 1981). Consequently more research on the topic is called for. A controlled laboratory study to do just that is described next.

Cold Pressor Experiment Methods

For a second laboratory experiment, the goal was twofold. First, the goal was to test any difference brand-name versus generic medications on medical outcomes via a placebo response. Secondly, the plan was to develop an experimental procedure that could act as a platform for many future experiments. Ideally this platform would allow testing of the placebo effect within an active drug effect. The shock procedure would not satisfy the second goal since for the most part only opioid drugs are thought to have an effect on that type of pain. There was also a consideration of using a lidocaine skin cream, which may have effect on electric shock pain, however it was determined that since there is no lidocaine skin cream with a well-known brand name, that this would not be the best manipulation. On the other hand, oral acetaminophen has been shown to significantly reduce pain from the cold-pressor test, although its effect may be modest and stronger with dosages above that typically given (Yuan et al., 1998). Therefore the decision was to use acetaminophen and the cold pressor test, in an effort to study a system with a real but small drug effect. Such a system could be an ideal platform for future studies, because a small drug effect could be manipulated by placebo manipulations, and would not be so strong that it would have a ceiling effect on which brand or price could have no effect.

For the cold pressor study, subjects were recruited by a posting to list-serves affiliated with the university, meaning that a large percentage of subjects were undergraduates. Subjects were, as before, told that the study had to do with how a person's past history of

painful experiences related to their current response to pain-reducing medications. Eligible participants were people who did not report high blood pressure (because of the potential of the cold pressor test to raise blood pressure), did not drink 3 or more alcoholic beverages per day (because of the potential for liver disease, in which case someone should not take acetaminophen), did not have any cardiovascular, pulmonary, metabolic, or liver disease, and was not allergic to over-the-counter pain relievers. Subjects were paid \$30 for participation, and the entire experiment lasted under one hour. Subjects gave informed consent for the procedure. The consent forms for the two conditions differed by only one line: whether they said the subject would take 'acetaminophen' or 'Extra-Strength Adult Liquid Tylenol.' Neither statement involves deception.

This study was run in an experimental room in the Media Lab. The room was set up with the experimental apparatus and was otherwise bare, except for biology-related textbooks on the shelves. The temperature in the room was slightly warm due to the heat output of the cooling machine. 100 subjects were run by the primary experimenter and 33 by one of two undergraduate assistants using the same experimental script.

In this experiment, subjects performed the cold pressor task two times, before and after ingesting the medication. In order to be absolutely certain of therapeutic equivalence, subjects were always given the same medication. This was extra-strength adult liquid Tylenol, either in its original packaging or re-packaged into a generic pharmacy bottle that simply read "acetaminophen." In this way there were no differences between the medication given to subjects except for the presence or absence of a brand-name, as seen in the photo below.



Graphic 2: Tylenol was presented to subjects either in its normal liquid, extra strength container or in a generic pharmacy container reading “acetaminophen. Use as directed.”

For the cold pressor task, subjects placed their hand in a small tub of water held constant at 4° C by a Neslab R100 circulating water chiller. Subjects placed their left hand in the water, with the water line coming up to approximately just past the knuckles. The forearm rested on the rim of the machine to reduce muscle strain.

During the time that the subject’s hand was in the water, they made ratings of their discomfort on a tablet computer to their right. Every 10 seconds, a visual analog rating screen appeared, anchored to the left with ‘no pain’ and to the right with ‘extreme pain.’ Subjects made ratings each time that the screen appeared by dragging a slider which defaulted in the middle, with a stylus, as seen in the photo below. Ratings on this visual analog scale were later converted to a 1000-point scale for analysis.



Graphic 3: The subject placed their left hand in the tub of cold water while using their right hand to make painfulness ratings on a computer screen.

Subjects were instructed to remove their hand from the water when their discomfort level reached a subjective 8 out of 10. If subjects never reached this level, they were automatically asked to remove their hand from the water after five minutes as a precaution against injury. The time until hand removal was recorded by the experimenter with a stopwatch. Following removal of the hand, subjects made one final rating on the computer, about their overall discomfort during the task. Towels were provided to dry the hand.

After this first cold pressor task, subjects took the medication. Subjects were given 500mg in 2 tablespoons of the liquid Tylenol, which is the normal recommended adult dosage, in a disposable plastic medicine cup. Half the subjects saw the liquid poured from the normal Tylenol container, and the other half saw it poured from a generic pharmacy container. The bottle was left in view of the subject for the entire experiment. Subjects were also offered a cup of water along with the medication which most accepted. (Note that although keeping the bottle in view of the subject during the experiment made it impossible to blind the experimenter to the subject's condition, it was felt that this step was necessary to remind subjects of the brand/generic condition, and the experimenter was careful to remain silent during the cold pressor task to avoid biasing the results.)

Next subjects waited 20 minutes. (The onset of analgesia has been determined to be somewhere between 15 and 90 minutes and it is known that onset time is shorter in an effervescent solution than in tablet form (Moller et al., 2000) During the 20-minute

waiting period, subjects simply did whatever they wished, usually reading or checking email. Following the waiting period, the cold pressor task was repeated exactly.

For the final 39 participants, an additional set of ratings were introduced. After removing their hand from the water, subjects made the overall rating, and then for an additional 60 seconds make discomfort ratings with their hand out of the water, resting on the rim of the chiller. At the conclusion of the one minute, subjects also made an overall discomfort rating for the time out of the water. The reason for this addition was the anecdotal implication by subjects that the effect might be stronger when their hand was already out of the water.

Finally, after the second cold pressor task, subjects completed the questionnaire, were paid, and left.

Cold Pressor Experiment Results

Description of the Subjects

In March and April 2008, a total of 133 subjects participated in the experiment. 65 of these (48.9%) were in the generic condition, and 68 in the brand condition. The mean age was 21.89, ± 6.05 . 71 (53.4%) of the subjects were female.

Subjects' Attitudes Towards Generics

Subjects' attitudes towards generic medications were similar to the general population (as discussed earlier). On the two questions asking how well generics compare to branded medications, subjects were favorable but not completely confident, rating them about 5 out of 7 (see table below). On the other hand, when asked about purchasing tendencies, subjects did not indicate that they heavily favored branded products, saying their tendency to buy and choose brands was only about 3 out of 7. (See appendix for exact question wording).

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
Effective	132	2.00	7.00	5.5303	1.25667
Standards	132	2.00	7.00	5.0909	1.28678
Buybrand	133	1.00	7.00	3.4286	1.91993
Choosebrand	133	1.00	7.00	2.9624	1.98252
Valid N (listwise)	132				

Table 2: When asked how well generics compare to brands, subjects rated about 5 out of 7; when asked if they tended to purchase brands, they rated it about 3 out of 7.

Time Course of Pain Ratings differs by Condition

Subjects' pain rating data did not increase purely in a simple linear fashion. After a period of time many subjects began to reduce their pain ratings, verbally describing this point as where their hand went numb. In fact, a repeated measures ANOVA of pain

ratings shows that there are both significant linear and quadratic components to the rating scores.

Subjects rated their pain every 10 seconds (in reality, due to differences in the length of time it took a subject to make a rating, this figure is approximate). When considering the change in pain ratings over time (i.e. the first rating, second rating, and so on, such that rating 6 took place after approximately one minute), cold ratings for all subjects shows the linear component to be significant. For the first 10 ratings of the second round, which includes 71 subjects, $F(1,70)=137.38$, $p<.001$. For the quadratic component: $F(1,70)=69.60$, $p<.001$. For the first 20 ratings, which includes 59 subjects, the linear component is $F(1,58)=33.95$, $p<.001$, and the quadratic component is $F(1,58)=96.29$, $p<.001$.

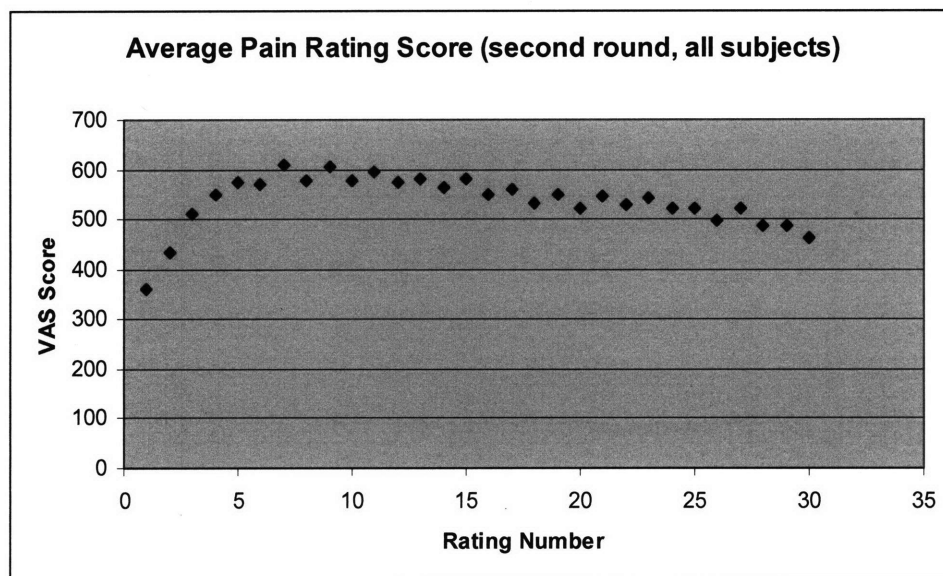


Figure 5: The average pain rating score for all subjects, over time.

Interestingly, the point at which this numbing effect occurs differs between the two conditions, and is earlier in the brand condition. In the generic condition, the point at which a subject first made a rating that was lower than the previous rating during the second cold pressor test (if this occurred) was the 6.24th rating made (stdev 3.10). In the brand condition, however, this point came earlier, after the 4.3rd rating (stdev 3.70). This is significant, $t(75)=2.48$, $p<.05$. (See figure below).

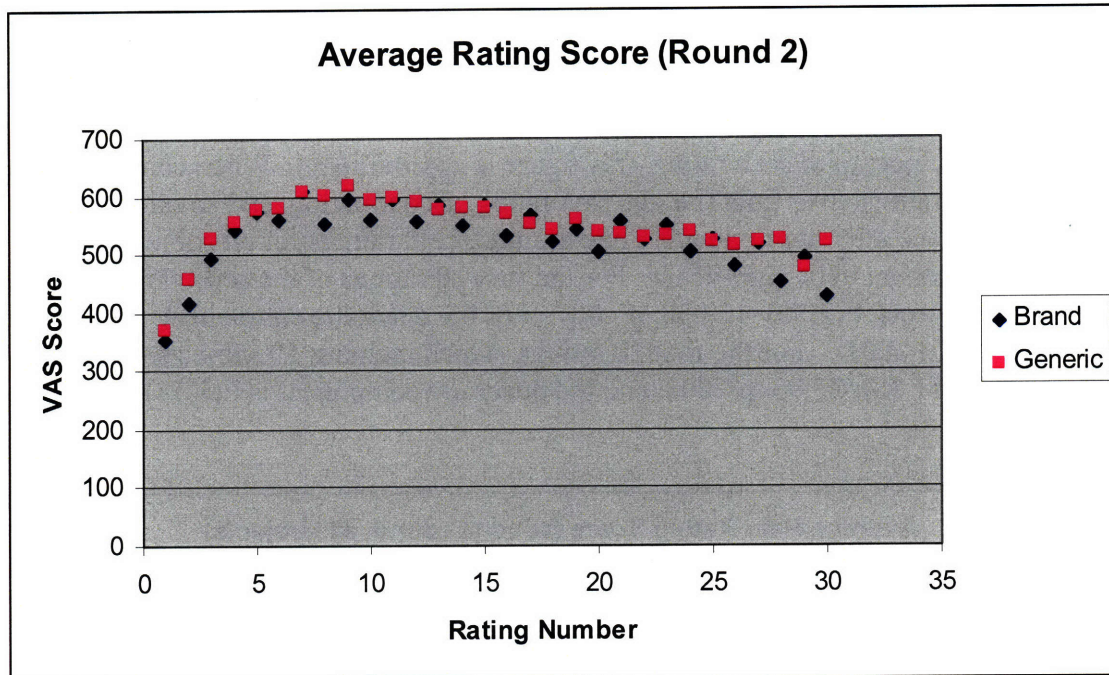


Figure 6: The average pain rating score for all subjects broken up by condition, over time. The brand-name subjects begin to lower their pain ratings earlier than the generic subjects (the 4.3rd rating versus the 6.24th rating).

Note: the variance in the brand condition appears greater than in generic, and in fact for several ratings, it is significantly greater: rating 20, 22, 24, and 30.

Cold Pressor Time may be Increased by Brand Only in Extreme Responders

Recall that a mandatory 5-minute maximum time limit on the cold pressor was built in to the protocol. Unexpectedly, a large number of subjects reached this cutoff; 42 (31.6%) subjects reached 5 minutes on the first round (and second round) of the cold pressor and were instructed by the experimenter to remove their hand at that time. An additional 12 individuals did not reach 5 minutes during the first round, but did reach the 5-minute ceiling during the second round.

The cold pressor test is typically measured by the amount of time that a person is able to keep their hand in the cold water. The variable referred to hereafter as Time_Difference is the time the person held their hand in the water during the second round minus the time held in the water during the first round, so that a positive number represents their time being increased after taking the medication. This variable however can only be accurately measured among subjects never reaching the 5-minute cutoff, of which there are 79 in total, 40 in the generic condition and 39 in the brand condition.

Overall, Time_Difference was modest. Among the 79 subjects the mean was 17.19 ± 50.20 . This 17.19-second difference is however statistically different from 0, $t(78)=3.04$, $p<.01$. Among these 79 individuals, there is no difference in

Time_Difference between conditions. In the generic condition subjects increased the length of time in the water by $13.37 \text{ seconds} \pm 47.06$, while in the brand condition the increase in time was $21.10 \text{ seconds} \pm 53.55$, $t(77) = .648$, $p = .498$.

However, the above analysis excludes by definition those subjects with the strongest reaction to the medication, those subjects who did not reach 5 minutes the first round, but did the second round. Subjects' length of time in the water was not normally distributed. Instead, there were two separate groups of subjects, those reaching 5 minutes, and those not reaching 5 minutes, with the mean at 17.19 seconds and a positive skew (see figure). Subjects in the 'cutoff' group were comfortable enough that that would have lasted indefinitely without experimenter intervention, as the mean last pain rating score they gave was only 577.69 ± 179.36 in the first round and 457.88 ± 186.02 in the second round.

The two histograms below show length of time in the water for both cold pressor rounds to show that, rather than being normally distributed, length of time in the water can be broken up into 2 groups of subjects.

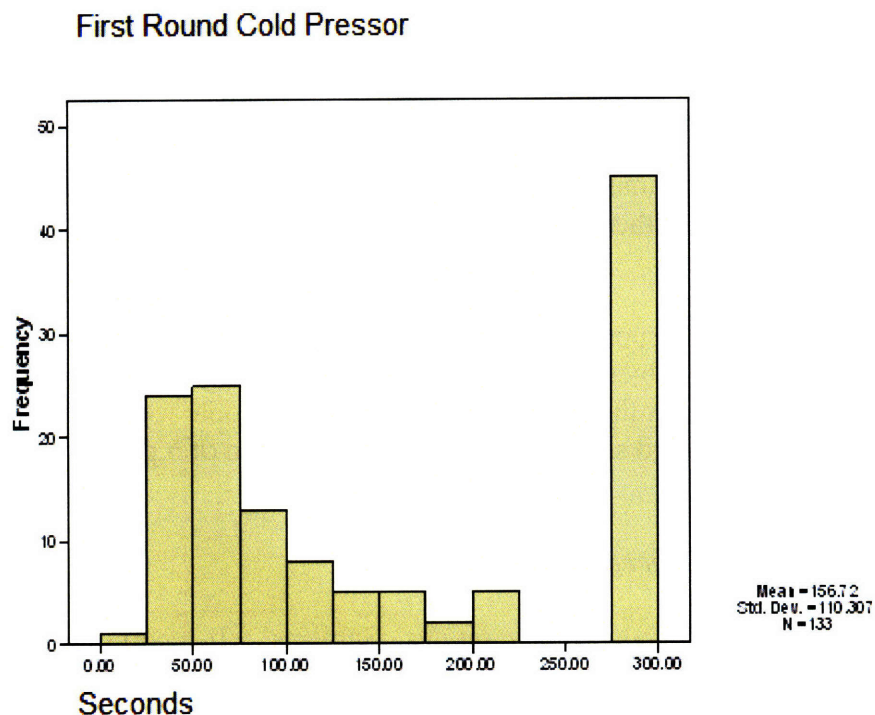


Figure 7: A histogram of the average time of the cold pressor test (in the first round) shows that there are two types of subjects, those reaching the maximum length of time (300 seconds) and those not.

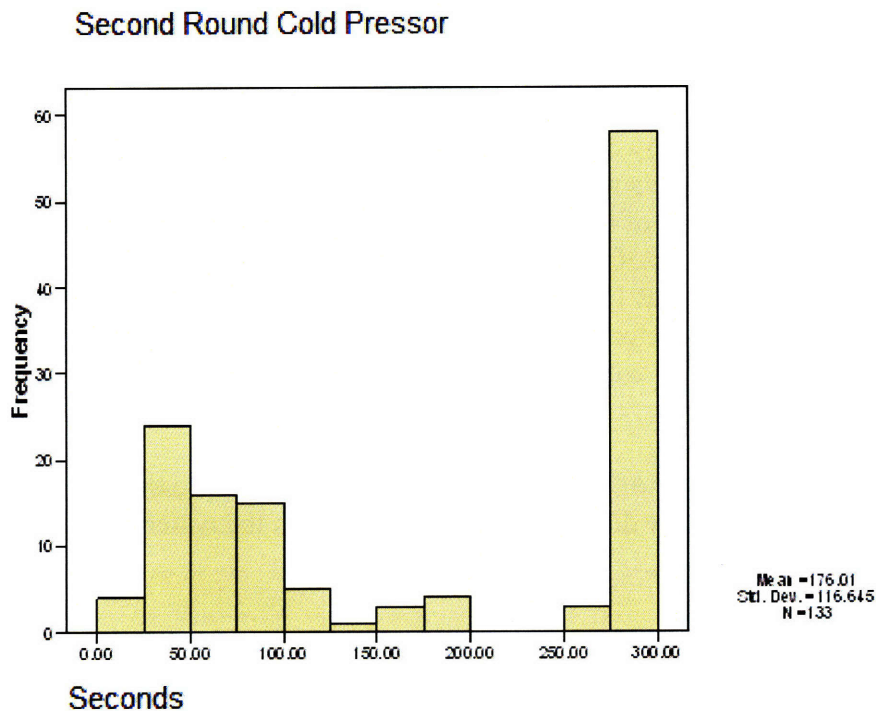


Figure 8: A histogram of the average time of the cold pressor test (in the second round) is similar to the first round, and shows that there are two types of subjects, those reaching the maximum length of time (300 seconds) and those not.

Because subjects are not normally distributed, those 12 subjects who switched from one category of responder to another can be considered “extreme responders” to the medication.

It is among these extreme responders that brand does display superiority over the generic condition. Among the 12 subjects who did not reach the 5-minute cut-off during the first round, but did reach it during the second round, 9 of these people were in the brand-name condition. This trends toward significance for the expectation of 6 people in each condition, $t(11)=1.9$, $p=.082$.

Non-Brand Modifiers of Dependent Measures

Recent pain correlates with reduced pain ratings. Subjects’ self-report of the painfulness of their past week is positively correlated with a reduction in pain rating scores between the two rounds ($r=.235$, $p<.01$). Subjects reporting more pain during the second round had an average ‘painful week’ score of 2.2 on the 7-point Likert scale, while subjects reporting less pain during the second round rated their week as 2.80, $t(127)=-2.5$, $p<.05$.

An experimenter effect was found in the data. Of the 133 total subjects seen during the experiment, 100 were seen by the primary experimenter, and 33 were seen by one of 2 undergraduate assistants. The undergraduates were asked to assist in the interest of time and seeing as many subjects as possible, and used identical scripts. Unexpectedly, a

difference was found in the overall placebo effect between experimenters. A chi-square test of whether or not the subject lasted longer in the water during the second round, versus experimenter, shows significant results, Pearson Chi-square statistic = 5.64, $p < .05$.

Experimenter * Longer Cold Pressor time in Second Round

Count		Longer time difference		Total
		shorter time	longer time	
experimenter	notrebecca	13	20	33
	rebecca	63	37	100
Total		76	57	133

Table 3: This table shows how many subjects lasted longer on the cold pressor test in the second round compared to during the first round, which may be thought of as the overall placebo effectiveness of the medication. There was a difference between experimenters, with the main experimenter inducing a weaker placebo effect.

This unexpected result underscores a well-known aspect of placebo research, which is that subtle changes in environment or medical practitioner can have important effects. However, importantly, no difference was found on the variable of interest (brand versus generic) as a result of experimenter effects. The interaction between experimenter and condition in a univariate ANOVA of the longer time variable is nonsignificant, $F(1,129) = .020$, $p = .887$.

The Cold Pressor Test as an Experimental Task

The cold pressor as an experimental task was also analyzed. Males lasted longer than females on the task. During the first round males lasted an average of 182.49 seconds, and females 134.22 seconds. $T(131) = 2.57$, $p < .05$). There was no difference however on Time_Difference between rounds, between genders.

There was a great deal of variability between subjects in terms of the difficulty and painfulness of the cold pressor task. This is demonstrated first of all in the enormous range in length of time subjects remained in the water; the shortest time was 16 seconds, and the longest time was the mandatory 5-minute cut-off point. The mean time was 156.72 seconds in the first round and 176.00 seconds in the second round, with large standard deviations of 110.31 and 116.65 seconds respectively. This large variability is also seen in the rating scores made by subjects during the cold pressor task. It is easy to see this variability by plotting the percentage of ratings that a subject made below 600 (the VAS scale converts to 1000). The appearance of 3 peaks is quite interesting. It shows that many subjects rated everything low, below 600, while another peak of subjects rated everything quite high. A third peak around 50% is surrounded by a moderately normal distribution.

The percent of ratings made below "600" (out of 1000) for each subject in round 1 of the cold pressor test.

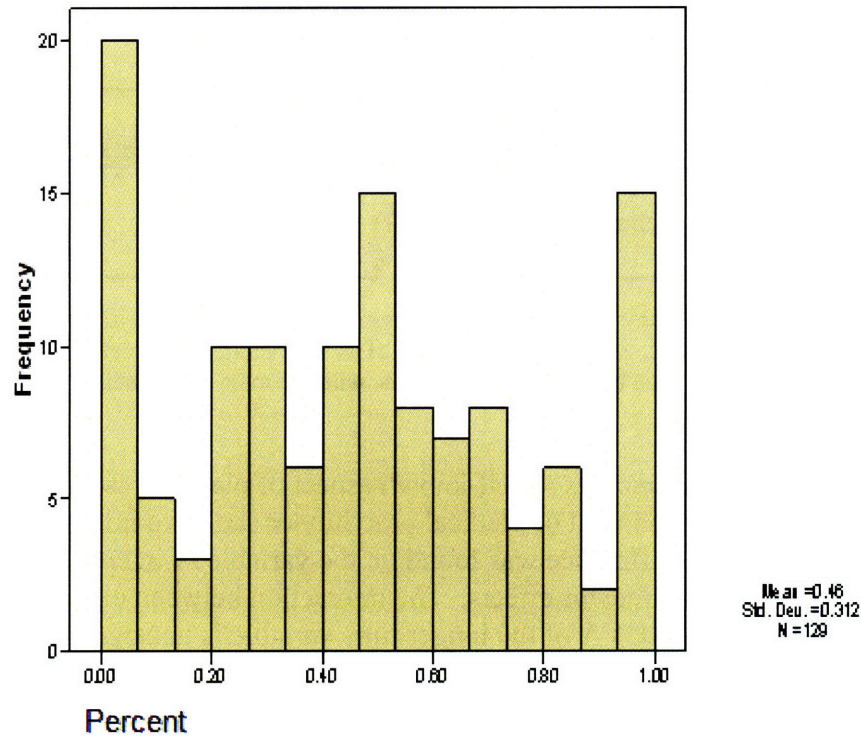


Figure 9: Histogram of the percent of ratings below 600, for each subject, during round 1 of the cold pressor.¹

¹ Although subjects were instructed to remove their hand upon reaching a subjective pain level of 8 out of 10, many subjects made ratings above 80% of the VAS line. In addition, a small artifact of increased ratings may be expected at 500 because this was the default rating.

The percent of ratings made below "600"
(out of 1000) for each subject in round 2 of
the cold pressor test

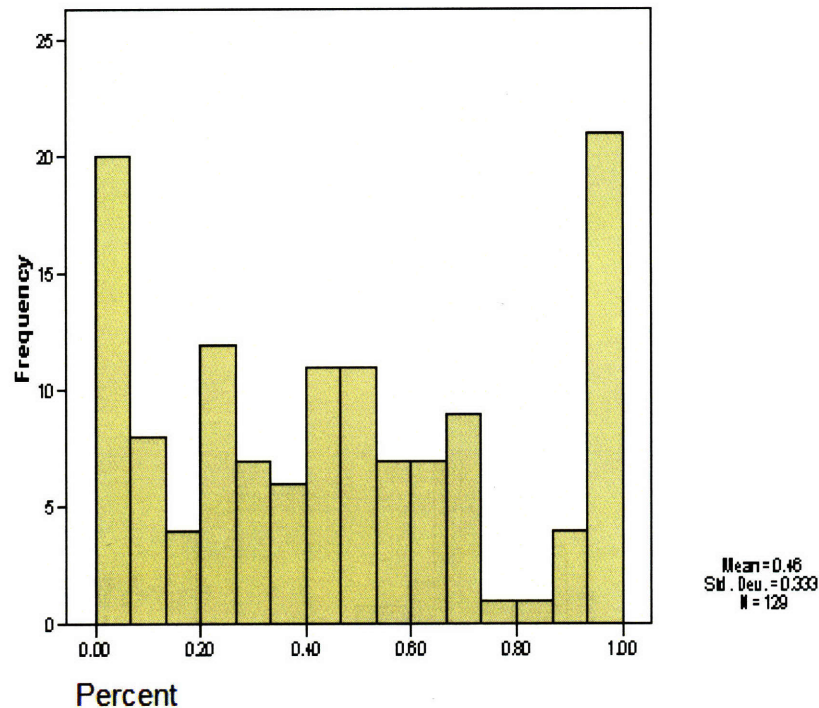


Figure 10: Histogram of the percent of ratings below 600, for each subject, during round 2 of the cold pressor.

Importantly, however, although there is great variability in subjects' response to the cold pressor task as a whole, the difference between cold pressor rounds is more defined. The difference in how many ratings were below 600 changes little between rounds, as seen in the figure below.

Difference between round 1 and 2 of percent of ratings below "600," for each subject

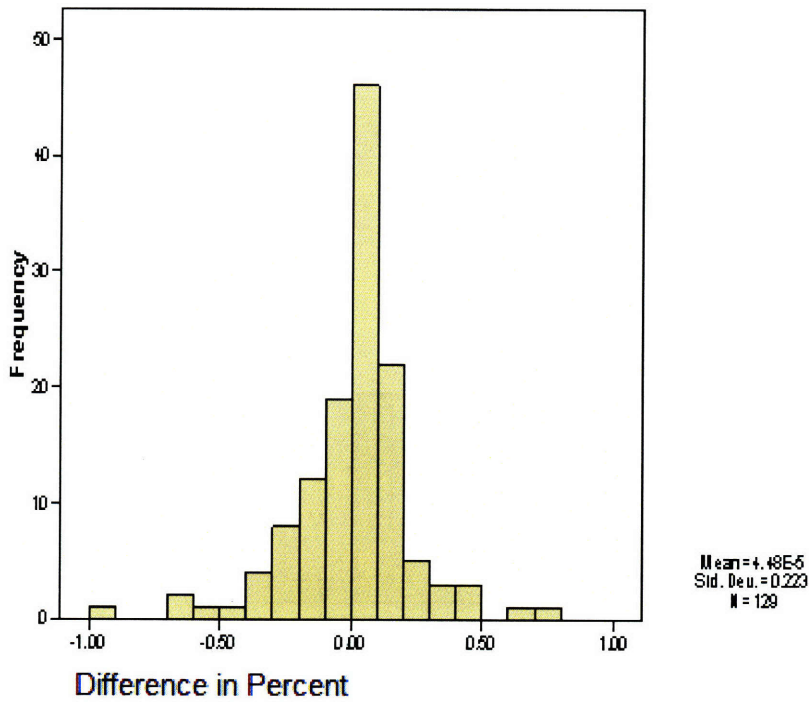


Figure 11: Histogram of the change in percent of ratings below 600, for each subject, comparing round 1 and 2 the cold pressor.

Cold Pressor Experiment Discussion

Discussion of Results

Due to the unexpectedly large number of subjects reaching the maximum cut-off point, it may be useful for future experiments to make the task more difficult by lowering the temperature from 4°C as it was here to 1 or 2°. It is also possible that this change might affect the linearity of the pain ratings. This lack of strict linearity was surprising both for the experimenters as well as perhaps for the subjects. One subject stated that “I was surprised by the temporal profile of the pain I experienced. I might have predicted the pain to rise monotonically, perhaps to a plateau, but instead I experienced an initial moderately high level of pain followed by a barely painful, numbed sensation and then a slower increase in pain back to moderate levels.”

The finding that the time course of cold pressor pain differs by condition is quite interesting. Because the two conditions do not differ in overall length of time or overall pain ratings, this finding does appear to be directly related the point at which subjects’ habituated to the water. Because the task overall was less difficult than anticipated and so many subjects were able to withstand the full 5 minutes of cold water, the habituation point may be a very useful measure of the effectiveness of the medication.

The idea that extreme placebo responses may be preferentially found in the branded condition is an interesting finding which highlights a potential new angle on placebo research, that of exploring the outliers in addition to the mean response. If it is possible to promote extreme placebo responses by controlling external factors, this could be particularly powerful.

The finding that recent pain is associated with a larger placebo response is particularly interesting because of the similar finding in the first laboratory experiment (Veladone). The fact that this variable seems important in both studies implies that it should receive more attention in future work. The unanswered question is why recent pain has an effect. One avenue might be through increased experience with pain relievers, leading to greater expectation. Another possibility is the interaction with temporary neurological alterations as a result of the recent pain.

Differences in experimenters or clinicians on placebo effects are well documented (Benedetti, 2002). Medical professionals are also aware of this fact. For instance, a nurse practitioner in pain management lamented the fact that some doctors did not present medical treatments with much confidence to patients, and she worried about the consequences of such a speaking style (anonymous, personal communication, March 2 2008). The fact that an experimenter effect surfaced here regarding the average amount of time in the water should remind experimenters to exercise caution in interpretation when there are multiple experimenters and to remember that in the clinical world this becomes an extremely important issue. Any effects established in the laboratory are then subject to the variations of the clinicians who in the real world administer any treatment.

One of the goals of this experiment was to see if the cold pressor paradigm used here is a suitable method for studying the placebo effect of marketing. The results of this experiment do not tend to support this goal because of the lack of strong impact of the medication on time or rating differences. It seems likely that because the cold pressor test is an unfamiliar procedure that expectations regarding the efficacy of OTC pain relievers were weaker than they would have been if the manipulation involved quotidian concerns such as headache, where consumers have experience with the effect of acetaminophen. The fact that the overall time difference between rounds was so low, only 17.19 seconds, presents a problem for studying the modification of placebo effects by marketing, because if there is very little effect possible, then it is difficult to study a modulation of that effect. Because of this, the laboratory cold pressor test does not seem the most satisfactory method to use as this research field moves forward. Ideally, future studies will involve more clinical environments, where the expected effect of the medication is more explicit, so that patients and consumers will be well acquainted with the medical problems and effective treatments before these treatments are modified on the aspects of price, brand, and so on.

Limitations of the Study

Certain design choices in the cold pressor study may have influenced the overall results. One important issue was the use of liquid Tylenol rather than pills. This was a logistical

necessity due to the inability to obtain pills without the branded logo yet identical in composition to the brand. Normally both a placebo and an active drug can be made up by a pharmacy in identical, non-branded capsules, but since here the goal was to use an explicitly branded pill, this was not possible. The use of liquid medicine allowed the Tylenol to be simply poured as necessary into a different, generic container. However, it is certainly possible that both the overall placebo effect and the specifically brand effect may have been weaker with the liquid than it would have been with pills, because the average adult consumer is relatively unfamiliar with liquid analgesics. Indeed, a number of people commented that they hadn't taken liquid Tylenol since childhood. Since there is more habit and ritual associated with pills than liquid, this is a real concern (Kaptchuk et al., 2006).

A similar concern is that fact that the expected effect of the medication was not quite explicitly spelled out. Essentially, subjects had to realize themselves that taking the medication was expected to reduce their overall pain ratings/ allow them to remain in the water longer, but these effects were not specifically explained beforehand. It is possible that, unlike familiar situations such as when expects Tylenol to eliminate a headache or muscle ache, that subject expectations varied so widely that it affected the variability of the overall results, and hence the ability to discern effects of the condition.

Another issue was the waiting time. Although 20 minutes is within the range of what studies have determined to be the onset time for acetaminophen, a longer waiting time would have rendered this more unambiguous. In the Branthwaite paper, more effects of branding were found after one hour than after 30 minutes, for instance (Branthwaite & Cooper, 1981). Waiting a longer time could potentially have resulted in larger non-placebo drug effect. If so, this may also have eliminated another potential concern, that of an 'overpromise' effect. In the words of Kirsch & Weixel, 1988, "if the claims made for a placebo are too extreme, placebo effects may be less likely, as implausible claims are unlikely to influence expectancies (Kirsch & Weixel, 1988)." In fact, some individuals reported surprise that the medication had not had stronger effects against the pain, and even wondered if their expectation of greatly reduced pain had made the second round feel much worse. Moderate expectations can be confirmed by cognitive biases, which can help confirm beliefs and increase placebo effects, but very strong and unconfirmed expectation would seem to greatly weaken the originally held beliefs.

In another version of this experiment, it might be useful to consider using the opposite hand for the second round of the cold pressor task to eliminate the effects of a still-somewhat cold hand. It would also be very useful, although at the present time it proved to be logistically impossible, to run the two complimentary placebo cells (placebo Tylenol and placebo generic). Other possible variations would be to add an arm that included some type of cognitive load, such as a difficult math task. The idea might be that the cognitive load could increase the difference between the brand and generic conditions by impeding the application of the rational knowledge that generics are not inferior to brands. However, this arm would be difficult to interpret until the basic mechanism of any effect is well understood. Another, advanced version of the study would be to examine the time course. For instance, what would happen if a person was

given the generic, but then at the end of the waiting period, immediately before the second round, they were informed that the medication was actually branded Tylenol. Again, this would be extremely interesting, but at this point in time multiple explanations would be possible. A time-course study that involved fMRI analysis could be particularly enlightening.

Cold Pressor Follow-up Study

A follow-up questionnaire (see appendix) was emailed to participants between 2 and 4 weeks after their participation. Subjects were entered into a raffle for a \$25 amazon.com gift certificate for returning the survey. 34 participants responded (approximately a 1/3 response rate because at the time the follow-up was sent out only 94 subjects had participated). 15 respondents (44.1%) had been in the generic condition and 19 (55.9%) had been in the brand condition.

The questionnaire used 7-point Likert scales. One question aimed to see if there was a difference in *remembered pain* between the conditions. The question asked overall how painful the experimental experience had been. Subjects reported the experience as having been moderately painful, an average of 4.12 on the 7-point Likert scale, and there was no difference between the two conditions; $t(30)=.072$, $p=.943$.

In the initial analysis of the data, subjects' evaluation of the painfulness of their past week appeared to have some predictive power over the time difference between the two rounds. However, since the questionnaire was answered at the end of the survey, it was possible that the experiment itself affected the answer to this question. To determine subjects' report of how painful their last week was directly affected by the cold procedure, the follow-up questionnaire repeated this question. In fact, the painfulness of their last week did not differ between the questionnaire and the follow-up. $t(33)=.399$, $p=.692$, which implies that pain in the last week may have affected time difference, rather than the other way around, which is quite interesting. In addition, pain in the last week did not differ by condition, $t(32)=.986$, $p=.332$.

Subjects were also asked how well they believed the medication to have worked on the pain of the cold water. In general, the ratings were not high; 2.67 with a standard deviation of 1.59, out of 7 points. In addition, there was no difference between conditions, $t(32)=1.284$, $p=.208$.

On the follow-up survey, subjects were also asked to write in what medication they took during the study. People in the brand condition remembered what drug they took more than people in the generic condition did. In the generic condition 5 out of 15 people, when asked what they took, were incorrect (such as saying aspirin) or didn't know (saying, for example 'generic pain reliever'). In the brand condition only 2 out of 19 did not know what medication they ingested, and this represents a significant difference between conditions in being able to accurately remember what drug was taken, $t(32)=4.062$, $p<.001$. This is a very interesting result. It appears that while in the brand condition subjects were able to remember the familiar brand name, this was not the case in the generic condition and subjects could not remember it. This has interesting

implications for patients given generic medications by physicians, because if a patient does not know what medications they are taking, they are likely to feel less confident in them, and also would not be able to engage in dialogue and learning on the topic of their medications. It should be noted that as the bottle was in plain view of the subjects throughout the entire experiment, there was adequate time for participants to learn the name.

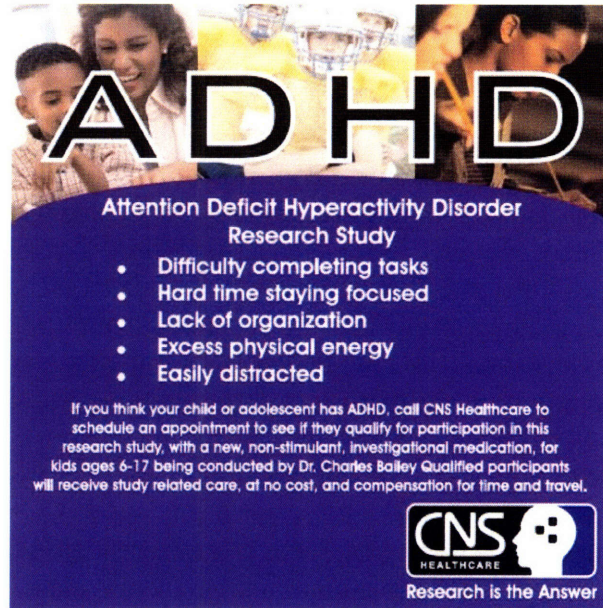
Non-Commercial Forms of “Marketing”

The ability of price, brand, advertising, or other forms of marketing to affect the placebo effect is dependent on how a person interprets and internalizes this information, and yet this too is complex. One issue concerns labels. At a certain level, a society as a whole is responsible for the pathologification of many diseases, drawing a line in the sand between acceptable variation and disease. For this reason, the labels given to a disorder can be thought of as a form of marketing in itself. As another example, the way that symptoms are presented or the environment in which they are asked about may impact their meaning. In two survey-based experiments, these concepts were explored.

Biased judgments of self-ratings

An above-average bias is a well-known finding in psychology. There are many studies that state that for many positive attributes, the majority of people rate themselves as above average. (Of course, if the average is taken to be the mean and the distribution is skewed, it is possible for the majority of people to be above the mean, but exception is generally disregarded). Less attention however has been given to self-comparisons on negative personal attributes or on a potential below-average bias effect, although this has been given some recent attention (Moore, 2007).

The marketing for medical treatments often come in the form of asking consumers if they possess several negative attributes. In the case of ADD/ADHD, for instance, advertisements for joining a medical study often ask consumers if they are “inattentive, restless, distractible”, and so on, as below, statements which implicitly ask about a comparison with other people.



ADHD

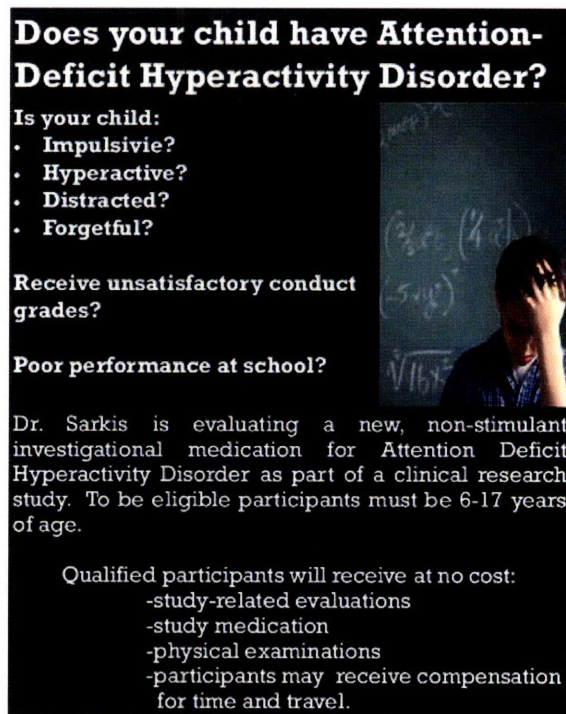
**Attention Deficit Hyperactivity Disorder
Research Study**

- Difficulty completing tasks
- Hard time staying focused
- Lack of organization
- Excess physical energy
- Easily distracted

If you think your child or adolescent has ADHD, call CNS Healthcare to schedule an appointment to see if they qualify for participation in this research study, with a new, non-stimulant, investigational medication, for kids ages 6-17 being conducted by Dr. Charles Bailey. Qualified participants will receive study related care, at no cost, and compensation for time and travel.

CNS
HEALTHCARE

Research is the Answer



Does your child have Attention-Deficit Hyperactivity Disorder?

Is your child:

- Impulsive?
- Hyperactive?
- Distracted?
- Forgetful?

Receive unsatisfactory conduct grades?

Poor performance at school?

Dr. Sarkis is evaluating a new, non-stimulant investigational medication for Attention Deficit Hyperactivity Disorder as part of a clinical research study. To be eligible participants must be 6-17 years of age.

Qualified participants will receive at no cost:

- study-related evaluations
- study medication
- physical examinations
- participants may receive compensation for time and travel.

Graphic 4: Advertisements for enrollment in ADHD research studies ask participants if they or their child are “impulsive, forgetful, easily distracted” and so on, which necessitates an interpersonal comparison.

This format of asking about symptoms can be problematic if there is an above-average effect for this type of negative attribute. Therefore a survey was developed to explore if an above-average bias might play a role in a person worrying about having ADD, as opposed to believing that their personal level of concentration, restlessness, etc, is normal or represents normal variation within the population.

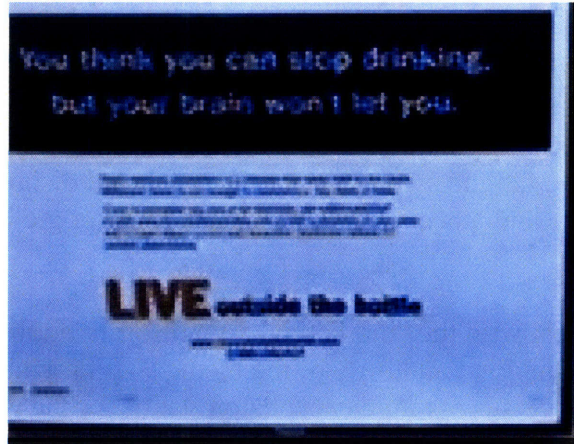
The full survey can be found in the appendix. It included distractor questions to reduce demand effects, and asked subjects to rate how they compared to peers on various attributes on a 9-point Likert scale. It also asked about several disorders (including ADD/ADHD) and if the person a) had ever considered that they might have it b) if others thought the person had it and c) if they were formally diagnosed with it. In 79 surveys conducted among MIT students in a public area at lunchtime in return for a large cookie, it was found that subjects rated themselves above the expected mean on restlessness and distractability, which fit the hypothesis that the baseline assumption of people may be that they have more of these qualities than average. On the other hand however, subjects rated themselves as having more ability to concentrate, and also as being less inattentive and less disorganized than others (see appendix for exact statistics). Thus while some attributes varied from the expected, they did not all vary in the expected direction.

Therefore, a second run of the survey was done, in a different environment. 46 surveys were filled out by students at the conclusion of a large lecture class. The hypothesis was that an experience in which concentration may be difficult (class) might affect self-comparisons on these attributes (although this should be irrelevant because the questions refer to trait, not state attributes). In this set of surveys, subjects said they were above average for impulsivity, restlessness, and distractibility, below average on inattention, and average on ability to concentrate. In other words, after class (compared to at lunch) students judged themselves to be more impulsive and trended to say they had worse ability to concentrate ($t(122)=1.9, p=.05$, $t(122)=1.8, p=.07$). The two sets of students did not differ in terms of age or gender (mean age 21.56 and 22.48, gender 53.2% and 48.9% female). While it is naturally possible that some of these students are in fact below or above average on the attributes inquired about, it is interesting that there were systematic changes as a result of the environment they were in when asked about it. And while 23.4 percent of the sample said that they had considered that they might have ADD, only 2.4% had actually been diagnosed with it, implying that this worry may indeed be cognitive bias and not reflect reality.

Many people suggest that the number of people diagnosed with, and medicated for, ADD is much higher than it should be. In order to obtain more accurate results from self-report measures therefore clinicians and school counselors making initial diagnostic judgments should take into account the environment in which the subject is making self-evaluations, and be aware that people may be overly concerned due to inaccurate judgments of how their behavior compares to others.

Effect of 'Biological' Labeling

Currently, researchers strive to understand the biological underpinnings of all disease, and understanding the neurological and biological causes for a disorder gives it more credence and weight. Being given a biological explanation for a disorder, even one as vague and inaccurate as "chemical imbalances in the brain," might possess significant meaning for patients. In the advertisement below, for example, the 'brain' is externalized from the identity of a person, seemingly to reduce feelings of guilt in the disorder.



Graphic 5: “You think you can stop drinking, but your brain won’t let you.” This advertisement for an alcoholism treatment medication tries to separate the person from the disease.

Similarly, a recent paper found that explanations of psychological phenomena were judged more satisfying by experts when they included irrelevant neuroscience information (Weisberg, Keil, Goodstein, Rawson, & Gray, 2008).

To examine how a biological label might impact judgments of a medical disorder, a survey was conducted among 109 individuals on the MIT campus. (See appendix for full questionnaire). In the survey, respondents read a story about their neighbor being diagnosed with a disease, and then made judgments about what could have caused the disease, how the neighbor should treat it, and if the neighbor should see another doctor. The only difference between conditions was the label given to the disease, which was a true label in all cases. 34 subjects received the label of chronic fatigue syndrome, 37 subjects read myalgic encephalomyelitis, another name for the same condition. 38 subjects read merely that the neighbor had a specific, unnamed disease. Subjects answered on a 7-point Likert scale ranging from 1, Definitely don’t think so, to 7, definitely think so.

The two names for the disorder differ in that while the first has behavioral connotations, the latter invokes a biological root. In fact, the different label for the same condition altered what subjects considered possible causes for the disorder: myalgic encephalomyelitis, compared to chronic fatigue, was more attributable to allergies (chronic mean 2.76, myalgic mean 3.58, $t(70)=2.68$, $p<.01$) and adrenal/endocrine disorder (chronic mean 3.50, myalgic mean 4.25, $t(70)=2.52$, $p<.05$). On the other hand depression trended toward being a possible player in causing chronic fatigue (chronic mean 3.86, myalgic mean 3.22, $t(70)=1.84$, $p=.070$), and counseling was thought to be a potential treatment only for chronic fatigue (chronic mean 3.30, myalgic mean 2.43, $t(70)=2.68$, $p<.01$). In addition, respondents trended to be more likely to advise the neighbor to get a second medical opinion when they were diagnosed with chronic fatigue versus myalgic encephalomyelitis (chronic mean 5.92, myalgic 5.40, $t(73)=1.68$, $p=.098$).

One potential limitation of this survey was the fact that respondents may have been more familiar with the term “chronic fatigue” than “myalgic encephalomyelitis,” and that this may have affected their response. In fact, neither disorder was very familiar to respondents, but myalgic encephalomyelitis was rated less familiar than either the disorder labeled “chronic fatigue syndrome” or the unlabeled disorder (mean familiarity rating for chronic fatigue and ‘specific disorder’ 2.40, for myalgic 1.55, $F(2,111)=5.23$, $p<.01$.)

Both of these surveys deal with the “marketing” of a disorder not by a pharmaceutical company per se, but by the joint authority of the medical community. The naming of a disorder chronic fatigue versus myalgic encephalomyelitis, or the way that a symptoms of ADHD are worded, may be extremely relevant to patients’ belief in their diagnosis and treatment. These factors too much be considered along with more traditional types of marketing for a complete picture of the role of information on direct drug effects.

Overall discussion

Implications for marketing

The implications of this research are very much in the hands of everyday people, both medical professionals and businesspeople. The most important take-away message is that it is important to be aware of how factors external to the medication, such as marketing, can impact perception and outcomes.

It is known that physicians are in a position of power in terms of providing information to subjects, and that the way they provide this information may impact patients’ results (Benedetti, 2002). However, physicians are not the only ones in a position to make such a statement. Essentially, advertisers do so as well. It is clear that advertising not only influences perception but also that direct-to-consumer advertising does indeed influence patients’ requests for medicines, and physician’s prescribing of medicines is heavily influenced by patient requests (Kravitz et al., 2005). Advertising could potentially influence placebo responses in several ways. Firstly, by increasing belief in the product through brand recognition, as discussed earlier. Secondly, it could influence one’s motivation for the drug to work, for instance by increasing one’s unhappiness with a condition, and motivation may be an important covariate with placebo response (Irmak, 2005). (For instance, an advertisement could explain that restless leg syndrome is not only uncomfortable, but dangerous, or that heartburn can cause esophageal damage). An additional avenue is through the excitement and newness of a recently-introduced product. Patients may demand or simply have more faith in the newest wonder drug and feel they are being denied medical progress if they are prescribed a stand-by drug. Currently there is much debate on the Cox-2 scandals, and observers wonder why they were prescribed so heavily when for many patients a simple NSAID would have been equally effective (Rubin, 2005). Similarly, recent evidence that the drug Vytarin is much less effective than previously thought caused commentators to lament the fact that many doctors tried it first, before prescribing older, tried medications (Marchione, 2008). A question that is

left unanswered, however, is how this radically enhanced faith and belief in the new drugs may have actually impacted their effectiveness.

The aspect of this research that is groundbreaking is not the fundamental concepts contained within it. That placebo is based on belief, and that belief is affected by marketing, are both established. However the link between the two fields is novel, and it is quite interesting that this question has not before been investigated. The explanation for this gap may be the lack of communication and fraternity between the various thought communities involved. The idea that marketing and medicine may not be at odds, but that in a real way may together shape medical reality, is a foreign but powerful one.

The proscriptive implications of this research are not simple. The answer of course is not to willfully give out expensive placebos and expect the best. Instead, this research directs us on a course of action of taking into account beliefs, and doing what is possible to direct those beliefs in the most beneficial action within a medical procedure that is by itself effective. High prices in particular may actually be detrimental because of creating the necessity for price discounts, and this sharp contrast in price could be particularly damaging.

Overall, this research opens up the doors for what has the potential to become an extremely fruitful new field at the forefront of medicine, psychology, marketing, and anthropology. As the experiments presented in this thesis represent the mere tip of the iceberg, considerable future work is warranted to truly understand both the power and the boundaries of marketing's direct role on medical outcomes via the placebo response. There are opportunities as well. For instance, even if a drug was purchased on discount, the consumer can choose to leave the original price sticker on the product. On a different level, a pharmaceutical company can boast of large R&D costs in their promotional materials on even an inexpensive drug.

We can also use these placebo effects to our advantage by managing how we think about the prices of our purchases. When we buy something expensive, especially medicines, we can keep the price sticker on it to remind us of the cost and to think of it as having been expensive. On the other hand, if we buy one of these products at a discounted price, we should think of the item in terms of its original, non-sale price. The relevance of the placebo effect in the field of marketing is just beginning to be uncovered, and of course goes far beyond the pricing of products. Whenever a factor affects people's expectations regarding a product, placebo effects may be strengthened or weakened. This means that other ways to manage our own placebo responses is to control our own access to certain kinds of marketing or medical information. One of these ways is to not spend too much time or effort reading about all the potential side effects of a medication. Of course it may be important or necessary in some cases to be fully aware of potential side effects, but when side effects are mild, reading about them in depth will only increase the likelihood that they will be experienced. By the same token, reading positive marketing information from the company's whose medication you are using can strengthen your expectations regarding the product. The nocebo effect of price could potentially be attenuated by the temporal interval between purchase and use, due both to forgetting the

price paid and to the accounting procedures in play during a time-delayed purchase and consumption (Shafir, 2006). However, the effect of brand should be more continuous, because you are re-reminded of the brand each time you consume it, by the packaging.

Future Research

For the development of this research field, quite a number of experimental designs present themselves. Most noticeable is the need to research the effect of placebo manipulations in therapies that have established drug effects, but still a placebo component. Interesting and relevant candidates might include antidepressants, chronic pain, and other conditions. Studying these effects in patients is particularly important given that there are important differences between placebo effects in experimental and real settings, such as vast differences in desire/motivation for the treatment to work. Also, by exploring other medical conditions, it will be possible to study more objective clinical outcomes. Future research into pain conditions could also explore certain physical manifestations of anxiety/pain, such as pupil response (Bitsios, Szabadi, & Bradshaw, 2002), skin conductance, and hormonal changes.

One relatively simple way to design a “field” experiment might be to engage with a pharmacy to sell certain drugs at a discount to randomized patients. Seemingly independent of this “sale,” patients would be asked to participate in a follow-up phone interview of their condition. With any field experiment such as the above, compliance would become an issue. A particularly relevant question is if the brand or price manipulation would directly impact patient compliance, which it well might, and measures would have to be taken to account for this, such as weighing the medicine bottle after a set period of time.

Alternatively, if it were possible to add an additional arm onto a clinical trial of an already-approved medication, it would be possible to directly see the differences between the branded and generic treatment. An advantage to this method would be that it would be possible to do a 2X2 design of branded/generic and placebo/active, which would allow a quantification of the ‘brand’ component of the placebo effect within the overall effect. An additional layer upon such a design could be the effect of advertising. For instance, it is known that subconscious priming with an advertisement affects behavior (Fitzsimons, 2008), and so we could examine whether conscious or unconscious priming affected the placebo modulation. This is particularly important to inform policy on direct-to-consumer advertising.

One yet unanswered question is the interaction between consumer decisions and these marketing effects. For instance, what happens when consumers seek out discounts? In a hypothetical question given to people on a questionnaire, fully 83% of respondents in our survey stated that they would prefer to purchase discounted medications. This generally is to be expected, but what is interesting is the interplay between conscious decisions and desires (e.g. to get a bargain) and possibly subconscious biases (i.e. price-quality assumptions). Medical professionals also seem to be unaware of the potential nocebo effect of low price. In another survey conducted among 69 medical professionals and

medical students, 83.47 believed that the average physician would prescribe a discounted version of an analgesic, and 73% would choose a discounted medication for themselves. This was the case even though they believed in the placebo response, rating the effectiveness of a placebo at reducing pain as 5.07 on a scale of 1-10 (significantly different from a rating of 1, or no effect, $t=19.41$, $p<.001$). It would be interesting therefore to connect the placebo effects discussed here with consumers'/patients' conscious behavioral choices. For instance, are consumers who consciously seek out price-cuts sheltered from the price-placebo effect, or does it make little difference?

It is also very important for future research to explore the implications of the complex payment structure for prescription medications. Because patients often pay a fixed co-pay amount, future research must explore the interplay between sticker price and copay, as well as discount prices from situations such as drug assistance programs in which the brand medication is actually cheaper than the generic.

That objectively irrelevant factors may be capable of affecting a medication's efficacy must lead us to take note of the situational factors surrounding medical treatments, including its price. The malleability of placebo effects can be either a benefit or a detriment, depending upon how we manage that context, and for all its complexity, an understanding of how these external factors affect the placebo response is necessary to obtain a more complete picture of drug effects in consumers' lives.

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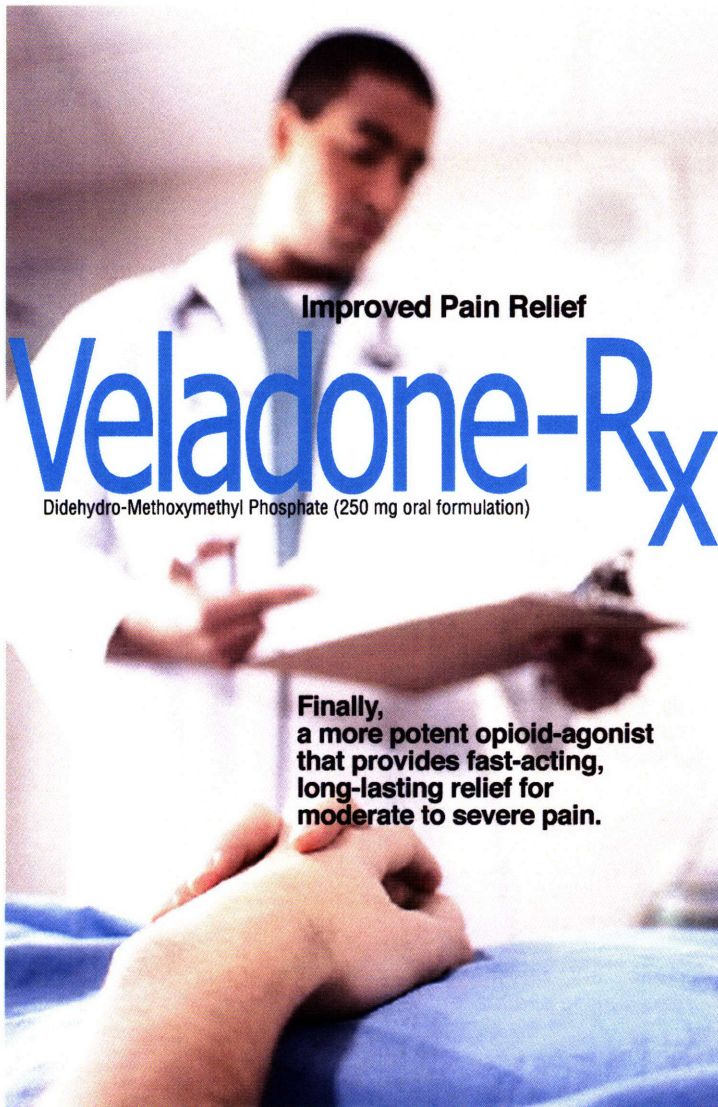
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Appendix

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Improved Pain Relief

Veladone-R_x

Didehydro-Methoxymethyl Phosphate (250 mg oral formulation)

**Finally,
a more potent opioid-agonist
that provides fast-acting,
long-lasting relief for
moderate to severe pain.**

Recently developed by Vel Pharmaceuticals in Cary, North Carolina, Veladone has proven highly effective in minimizing pain and allowing for increased patient mobility post-surgery.

Veladone is recommended for moderate to severe pain, including pain from:

surgery
muscle strains
dental infection and oral surgery
trauma

Veladone is an exciting new medication in the opioid family (the same class of drugs as codeine and morphine). Veladone is more effective than these older drugs due to a reduced hepatic (liver) metabolism, which ensures faster absorption into the body.

Clinical studies show that over 92 percent of patients receiving Veladone in double-blind, controlled studies reported significant pain relief within only 10 minutes that lasted up to 8 hours.

Side effects of Veladone are generally mild and include lightheadedness, dizziness, and nausea. Veladone is not recommended for pregnant or nursing women, or for patients with advanced kidney or liver disease.

Warning:
Veladone should not be administered to patients who have previously exhibited hypersensitivity to other opioid-derived pharmaceuticals.

Dosage should be adjusted according to severity of pain and patient response. Veladone is to be taken orally, generally one tablet every 8 hours as long as pain persists. Veladone may be taken with or without food. Dosage may be adjusted by a physician according to severity of pain and patient response. Do not exceed 8 tablets in a 24-hour period.

Veladone is manufactured and shipped from a temperature-controlled, state-of-the-art facility in Cary, North Carolina, USA. It is available by prescription exclusively from Online Pharmacy (<http://onlinepharmacy.com/Veladone-Rx>).

Cost	
1 Capsule	\$ 2.50 (+ \$1.25 shipping)
6 Capsules	\$13.50 (10% discount of the single capsule price + \$1.25 shipping)
12 Capsules	\$24.00 (20% discount of the single capsule price + \$1.25 shipping)
24 Capsules	\$42.00 (30% discount of the single capsule price + \$1.25 shipping)

Veladone is covered under most managed-care health plans.

Veladone is a product of Vel Pharmaceuticals,
Cary, North Carolina, USA

To receive more information,
please contact customer care via our website:
<http://onlinepharmacy.com/Veladone-Rx/info.html>

Veladone Questionnaire

ID _____

PLEASE be as honest and accurate as possible

Do you consider your life so far to have been:

- ☐ Relatively pain-free
- ☐ Moderately painful, with several painful experiences
- ☐ Moderately painful, with one or more chronic pains
- ☐ Very painful, with many painful experiences
- ☐ Very painful, with one or more chronic pains

In the past month, has your life been:

- ☐ Relatively pain-free
- ☐ Moderately painful, with several painful experiences
- ☐ Moderately painful, with one or more chronic pains
- ☐ Very painful, with many painful experiences
- ☐ Very painful, with one or more chronic pains

Today, aside from the experimental procedure, have you felt:

- ☐ Pain-free
- ☐ Mild-Moderate pain, such as a headache, bruise, sore muscle, etc?
- ☐ Severe pain

Which of the following experiences have you had?

	How many times?	How severe was your pain at the time of the event? (mild) 1 2 3 4 5 6 7 8 9 10 (extremely severe)	If you experienced pain after the event, for how long?	If you experienced pain after the event, how severe? (1-10)
<input type="checkbox"/> Car Accident				
<input type="checkbox"/> Surgery				
<input type="checkbox"/> Broken bone/torn ligament/bad sprain				
<input type="checkbox"/> Other serious accident				

	How often do you experience this?	How severe is the pain? (mild) 1 2 3 4 5 6 7 8 9 10 (extremely severe)
<input type="checkbox"/> Migraines or headaches		
<input type="checkbox"/> Back, joint, muscle pain		
<input type="checkbox"/> Arthritis, fibromyalgia,		
<input type="checkbox"/> Other chronic pain		

Do/did you engage in the following?

	Date began activity	Date stopped doing activity	Frequency of activity per week or month
<input type="checkbox"/> Play a painful sport? (football, wrestling, paintball, etc) Which?			
<input type="checkbox"/> Exercise to the point of physical pain?			
<input type="checkbox"/> Exercise to the point where you are very sore afterward?			
<input type="checkbox"/> Undergo training for the armed forces?			

Answer Yes/No for the following questions

I spend a lot of time around people who are in pain (as a nurse, caretaker of sick family member, etc) _____

I consider myself to be more anxious than the average person _____

Seeing painful experiences on TV, like a car accident or injection, makes me cringe _____

I think that "No pain, no gain" is generally accurate in life _____

I sometimes have to limit my activities due to physical pain _____

When you experience pain as a result of sport or exercise, do you normally see it as:

- ☐ An annoyance
- ☐ Something to be proud of- you really pushed yourself
- ☐ A challenge to deal with
- ☐ A sign of a possible problem- maybe a strain or stress injury
- ☐ Other: _____

When I am in pain, I usually:

- ☐ Am able to distract myself with activities or thoughts
- ☐ Am very aware of the pain until it subsides and find it difficult to do other things
- ☐ Other: _____

I consider myself to have: below-average average above average pain tolerance

(Women only) Have you undergone childbirth? NO YES How many times? _____

Do you experience menstrual cramps? NO YES How severe: (mild) 1 2 3 4 5 6 7 8 9 10 (extremely severe)

Given the choice between identical medicines, one made in the United States and the other in China, would you tend to prefer one over the other? NO YES

Why? _____

If you preferred the American-made medicine please answer the following:

If the medicine from China were half (50%) the price of the American version, would that change your opinion? YES NO

If the medicine from China were one-quarter (25%) the price, would that change your opinion? YES NO

How nervous were you about this experiment? (mild) 1 2 3 4 5 6 7 8 9 10 (extremely severe)

I take some form of **pain medication** at least: Daily Weekly Monthly Yearly Never

I take medication of any sort at least: Daily Weekly Monthly Yearly Never

Cold Pressor Questionnaire

ID _____

1. In an average month,

a) How many times do you take a prescription medication? _____

b) How many times do you take a non-prescription medication? _____

c) How many times do you take a non-prescription *pain* reliever? _____

2. To what extent to you agree with the following statements?

a) Generic drugs are just as effective as brand-name drugs

strongly disagree

1 2 3 4 5 6 7 strongly agree

b) Generic drugs are manufactured to the same standards as brand-name drugs

strongly disagree

1 2 3 4 5 6 7 strongly agree

c) I try to buy the brand-name version of a medicine whenever possible

strongly disagree

1 2 3 4 5 6 7 strongly agree

3. Given the choice between generic ibuprofen for \$5.50 and brand-name ibuprofen (like Motrin or Advil) for \$6.50, which do you choose?

Definitely the generic

1 2 3 4 5 6 7 Definitely the brand-name

4. How much physical pain have you experienced in your life?

Very little

or no physical pain

1 2 3 4 5 6 7 An extreme amount of physical pain

5. In the past week, how much physical pain have you experienced?

Very little

or no physical pain

1 2 3 4 5 6 7 An extreme amount of physical pain

6. Today, have you experienced any pain (muscle soreness, headache, etc) besides for during the experiment?

No pain

Some pain

much pain

7. What is your tolerance for pain?

Very low						Very high
1	2	3	4	5	6	7

8. How familiar are you with the brand Tylenol, made by Johnson & Johnson?

Not at all familiar					Very familiar
1	2	3	4	5	6
					7

Demographic Information

Annual household income: (if you are a college student, refer to your parents' household income)

☐ \$0-\$15,000

☐ \$15,000-\$29,999

☐ \$30,000-\$44,999

☐ \$45,000-\$59,999

☐ \$60,000-\$74,999

☐ \$75,000 or more

Gender F M

Ethnicity (circle all that apply): Asian Caucasian African-American
 Native American/Alaska Native Hispanic Other: _____

Age: _____

Cold Pressor Follow-Up questionnaire

1. What is your tolerance for pain?

Very low

1 2 3 4 5 6 Very high 7

2. In the past week, how much physical pain have you experienced?

Very little

or no physical pain

An extreme
amount of physical pain

1 2 3 4 5 6 7

3. What medicine did you take during the experiment? _____

4. How well did the medicine work at reducing the pain of the cold water?

It didn't work at all

It worked extremely well

1 2 3 4 5 6 7

5. What do you believe was the overall goal/purpose of the experiment? _____

6. What is the minimum amount of money for which you would repeat the experiment?

\$ _____

7. Overall, how painful was the experience?

Not at all painful

extremely painful

1 2 3 4 5 6 7

8. Was there anything about the experiment that surprised you, or you didn't understand?

2. Of these medications, how many are brand-name _____; are generic brand _____?

---Generic drugs are just as effective as brand-name drugs

1 2 3 4 5 6 7

(strongly disagree) (strongly agree)

---Generic drugs are manufactured to the same standards as brand-name drugs

1 2 3 4 5 6 7
(strongly disagree) (strongly agree)

---I know enough information about medicines to make a good decision between brand-name and generic drugs

1 2 3 4 5 6 7
(strongly disagree) (strongly agree)

--Price generally reflects the quality of a medicine, such that a more expensive medicine is likely more effective than a cheap medicine.

1 2 3 4 5 6 7
(strongly disagree) (strongly agree)

--I try to buy the brand-name version of a medicine whenever possible

1 2 3 4 5 6 7

(strongly disagree) (strongly agree)

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4. Have you ever switched from taking the *generic* to the *brand-name* version of the same drug?

No

Yes→

4a)Why: Medicine's effectiveness Medicine's side effects
 Cost Insurance coverage Other reason: _____

4b) After starting the new (brand-name) version of the drug, I was						
1	2	3	4	5	6	7
Much Less satisfied with				Much More satisfied		
the brand-name				with the brand-name		
than I had been				than I had been		
with the generic				with the generic		

4. Have you ever switched from taking the *brand-name* to the *generic* version of the same drug?

No

Yes→

4a)Why: Medicine's effectiveness Medicine's side effects
 Cost Insurance coverage Other reason: _____

4b) After starting the new (generic) version of the drug, I was						
1	2	3	4	5	6	7
Much Less satisfied with				Much More satisfied		
the generic				with the generic		
than I had been				than I had been		
with the brand-name				with the brand-name		

Age _____ Gender: M F Home Zip Code _____

Do you have any additional comments about generic and brand-name

medications? _____

Biased Self-Ratings Questionnaire

For all questions, please rate how you compare to your peers (people around your age with whom you work or go to school).

Rate the questions on the following scale:

Considerably below average

Considerably above average

1 2 3 4 5 6 7 8 9

1. Compared to your peers, how likely are you to have an aptitude for juggling (if you took lessons and practiced)? _____
2. Compared to your peers, how impulsive are you? _____
3. Compared to your peers, how good are you at concentrating when studying? _____
4. Compared to your peers, how restless are you? _____
5. Compared to your peers, how inattentive are you? _____
6. Compared to your peers, how good are you at getting along with others? _____
7. Compared to your peers, how good are you at telling when someone is lying? _____
8. Compared to your peers, how good a driver are you? _____
9. Compared to your peers, how disorganized are you? _____
10. Compared to your peers, how much do you know about World War II history? _____
11. Compared to your peers, how anxious are you? _____
12. Compared to your peers, how distractible are you? _____
13. Compared to your peers, how much do you know about TV soap operas? _____
14. Which of the following hobbies could you see yourself pursuing?(circle all that apply)

Rugby	gardening	origami	antique cars
Poetry	karate	meditation	painting
15. Age _____
16. Gender: F M

17. What is the highest schooling you have completed or are currently enrolled in? _____

18. Please make a check mark in any relevant boxes.

	Have you ever thought you might have	Have others ever suggested you might have	Have you ever been diagnosed with
ADD/ADHD			
Anxiety disorder			
asthma			
Autism spectrum disorder (including Asperger's)			
Irritable bowel syndrome			
Learning difficulties			
Sleep disorder			

Chronic Fatigue Survey (where it says “chronic fatigue” below, the other surveys say “myalgic encephalomyelitis” or “a specific disorder.”)

Imagine the following:

You run into your neighbor, who you’re somewhat acquainted with, while you are both setting out the trash. You strike up a conversation. Your neighbor tells you that they recently went to a doctor and were diagnosed as having chronic fatigue syndrome. They have felt extremely exhausted for about the past 7 months, and that resting doesn’t seem to affect how tired they feel. They tell you that they have a sore throat, tender lymph node in the neck, and general muscle pain. Their joints hurt but aren’t red or swollen. Most of these symptoms began simultaneously. The cause of this condition is unknown.

Now please answer the following questions the following scale:

Definitely don’t think so						definitely think so
1	2	3	4	5	6	7

1. Should your neighbor see another doctor? _____

2. Do you think their situation may be attributable to:

Lack of exercise	_____
Depression	_____
Neurological abnormalities	_____
Psychosomatic/psychological causes	_____
Viral or bacterial infection	_____
Stress or trauma	_____
Genetics	_____
Immune dysfunction	_____
Allergies	_____
Adrenal/endocrine disorder	_____
Nutritional deficiency	_____

3. Do you think the following treatment option might help your neighbor?

Vitamins	_____
Exercise	_____
Pain medication	_____
Anti-depressants	_____
Counseling/ “talk therapy”	_____
Meditation	_____

4. How familiar are you with this condition?

Not at all familiar						Very familiar
1	2	3	4	5	6	7